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GENETIC, NEURODEVELOPMENTAL AND PSYCHIATRIC STUDIES OF TURNER SYNDROME

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Cover illustration: Photo by Giovanni Cancemi Microscopic view of chromosome X

Genetic, neurodevelopmental and psychiatric studies of Turner syndrome

Thesis for Doctoral Degree (Ph.D.)

By

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To my family

Popular science summary of the thesis

Turner syndrome is a genetic condition that occurs approximately in 1 in 2000 born girls. This condition belongs to the group of sex chromosome abnormalities, where individuals have a different set of X and/or Y chromosomes. This thesis focuses primarily on the girls and women with Turner syndrome who have only one normal X chromosome (45,X) instead of the usual two (46,XX). Turner syndrome typically occurs when there is an error during the sorting of the dividing sex chromosomes, leading to the total loss or damage of one of the two X chromosomes. For the diagnosis of Turner syndrome, in addition to the genetic setting, there must be an impact on one or more of the body's functions, but this might not always be visible on the outside. An imbalance or total lack of sex hormones is almost always present in Turner syndrome, often requiring medical intervention for puberty to start. Girls with Turner syndrome are typically shorter than their peers from the age of five. Importantly, early detection and treatments can assist with initiating puberty and increasing height growth. It is, however, crucial to remember that there is considerable variation among individuals with Turner syndrome in terms of symptoms and challenges.

For many decades, research has shown that girls with Turner syndrome may find subject areas like mathematics more challenging than other subjects in school. While the intelligence of individuals with Turner syndrome, generally falls within the normal range, they may have strengths and weaknesses in specific domains. Specifically, one strength common among individuals with Turner syndrome are their verbal skills, but they tend to have weaknesses relating to non-verbal skills. Social skills and relationships with peers have been raised as challenges for some individuals with Turner syndrome. However, the extent of these different challenges and their underlying causes remain underexplored.

A higher prevalence of Attention Deficit Hyperactivity Disorder (ADHD) and Autism spectrum disorder (ASD) has been suggested in individuals with Turner syndrome compared to general population, but there is a limited understanding of the potential links between the conditions. Similarly, past research has highlighted higher risks of depression, anxiety, and other psychiatric symptoms among girls and women with Turner syndrome, but results are sometimes conflicting, and the majority of individuals with Turner syndrome report no challenges in these areas.

In this thesis the aim was to examine different aspects of cognition, neurodevelopmental and psychiatric disorders in individuals with Turner syndrome by various angles, using different methods. To further investigate mechanisms that may influence symptoms or challenges, we investigated whether the symptoms differ depending on genetic factors such as which parent the retained X chromosome origins from.

In **Study I**, we used linked Swedish population registers to cover all females diagnosed with Turner syndrome in Sweden. To examine if the 1392 females that were found with Turner syndrome had a higher risk of neurodevelopmental or psychiatric disorders we compared with a control group of 139200 females from the general population, matched in age and region born.

In **Study II**, we examined cognitive profiles of 30 women with Turner syndrome. We also examined whether there were participants that met the diagnostic criteria for ADHD and/or ASD and whether there were links between cognitive profiles and ADHD and ASD symptom severity.

In **Study III**, we explored learning and decision-making behaviors in 35 women with Turner syndrome compared to a control group. In an experimental task designed as an online game, participants received either social or non-social feedback on their choices. We then used computer-based modeling to explore potential underlying mechanisms.

In **Study IV**, 80 women with Turner syndrome answered a questionnaire about experiences and challenges during school age, current employment, education level, and whether they had a partner. We reviewed participants' medical records to examine the presence of diagnosed neurodevelopmental and/or psychiatric disorders. Furthermore, we collected blood samples from participants and their parents to conduct genetic analysis to determine the parental origin of the remaining X chromosome in the participant. Finally, we explored whether the origin of the retained X chromosome influenced the collected data.

Abstract

Turner Syndrome (TS) is a genetic condition characterized by the partial or complete loss of one sex chromosome. Associations with neurodevelopmental and psychiatric disorders has been suggested in TS, but findings are inconsistent. An uneven cognitive profile and challenges in social skills and executive function are described in TS but interactions between domains are unclear and studies in adult women with TS are scarce. It has been proposed that the phenotype of TS is affected by the parental origin of the retained X chromosome, but evidence is conflicting. Thus, the overarching aim of this thesis was to examine the neurodevelopmental, psychiatric, cognitive, and psychosocial aspects in TS. The methods used to achieve these aims were the following: **Study I**, a population-based retrospective cohort study using registers to examine associations between TS and diagnoses of neurodevelopmental and psychiatric disorders. **Study II**, a cross-sectional study where standardized questionnaires and psychological testing were used for assessments in adult women TS. **Study III** a cross-sectional case-control study with an experimental manipulation of social and non-social feedback in a reinforcement learning tasks, examining choice behaviors in adult women with TS. **Study IV**, a cross-sectional retrospective study where diagnoses were extracted from medical records, sociodemographic variables and school-age experiences was assessed in self-report questionnaires and the parental origin of the X chromosome was identified in molecular analyses for comparisons between groups. Findings revealed that Individuals with TS are at increased risk for certain neurodevelopmental and psychiatric disorders (**Study I**). The cognitive profile of TS in adulthood is associated with a clinically significant uneven cognitive profile, but the split does not correlate with symptoms of neurodevelopmental disorders (**Study II**). Social feedback in the reinforcement learning task led to a more explorative choice behavior in the control group compared to the group with TS, where no effects of social feedback on learning was found (**Study III**). No differences emerge based on the X chromosomes origin or karyotype (**Study IV**). Results in medical record review indicated a trend of increased number of diagnoses in depression, anxiety, and stress-related disorders in adult woman with TS and self-reported questionnaires revealed challenges academically and socially during their school age. However, the sociodemographic outcomes of educational achievements and occupation showed no differences compared to general population of adult woman (**Study IV**).

List of scientific papers

- I. **Björlin Avdic H**, Butwicka A, Nordenström A, Almqvist C, Nordenskjöld A, Engberg H, Frisé, L.

Neurodevelopmental and psychiatric disorders in females with Turner syndrome: a population-based study.

Journal of Neurodevelopmental Disorders. 2021;13(1):51.

- II. **Björlin Avdic H**, Kleberg JL, van der Poll M, Frisé L, Hutley M, Sarjanen M, Nordgren I, Ekholm K, Hirschberg AL, Nordgren A, Willfors C.

Cognitive profile in adult women with Turner syndrome: IQ split and associations with ADHD and ASD.

Cognitive Neuropsychiatry. 2023;28(3):207-25.

- III. **Björlin Avdic H**, Strannegård C, Engberg H, Willfors C, Nordgren I, Frisé L, Hirschberg AL, Guath M, Nordgren A, Kleberg, J L.

Reduced effects of social feedback on learning in Turner syndrome.

Scientific reports 2023;13(1):15858.

- IV. **Björlin Avdic H**, Wachtmeister A, Sahlin E, Willfors C, Nordenskjöld M, Frisé L, Engberg H, Hirschberg AL, Kleberg JL, Nordgren A.

Parental origin of the X chromosome in Turner syndrome: no evidence for impact on neurodevelopmental and psychiatric disorders, socio-demographic outcomes or adverse experiences during school age

Manuscript

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
AQ	Autism Spectrum Quotient
DAWBA	Development and Well-Being Assessment
EHR	Electronic Health Record
ICD	International Statistical Classification of Diseases and Related Health Problems
ID	Intellectual disability
LIS	Laboratory information systems
LMM	Linear mixed effects models
NPR	National Patient Registry
NPÖ	Nationell Patientöversikt (Swedish National Patient Summary)
OR	Odds Ratio
QF-PCR	Quantitative fluorescence-polymerase chain reaction
TS	Turner syndrome
WAIS-IV	Wechsler Adult Intelligence Scale, 4th edition

1 Introduction

The focus of this thesis is Turner syndrome (TS), a sex chromosome aneuploidy where one of the two X chromosomes is completely or partially missing. Sex chromosome aneuploidies are often associated with both neurodevelopmental and psychiatric disorders, but the genetic mechanisms behind different clinical, psychological, and behavioral manifestations in these disorders are still not fully understood (1).

TS was first described by Šereševskij, Ullrich and Turner in the 1920–1930s and was initially named according to different combinations of their names (2). The link between the 45,X genotype and the phenotype was not made until 1959 (3). Girls and women with TS exhibit a diverse spread of clinical manifestations with different degrees of severity in the affected individuals. The definition of the syndrome is that the individual has, in addition to the genotype, one or more specified clinical manifestations (1). Early loss of ovarian function, infertility (4), and short stature are the most common features of TS as well as some facial characteristics (1). Moreover, there is a higher incidence of congenital heart conditions and gastrointestinal diseases as well as endocrine, metabolic and autoimmune disorders in females with TS, and thus an increase in mortality compared to the general population (5–8). In addition, individuals with TS have an increased risk of hearing loss and impaired vision. As such, it is important to assess this at an early stage as it could be mistaken for learning difficulties or challenges in understanding social communication (9–11).

The aim of this thesis was to examine neurodevelopmental, psychiatric and cognitive aspects of Turner syndrome (Figure 1). A better understanding of the underlying challenges and comorbidities in Turner syndrome is crucial for early detection and development of improved treatment strategies. From a broader perspective, the overarching aim was to add to the existing knowledge concerning the impact of the X chromosomes in neurodevelopmental and psychiatric conditions.

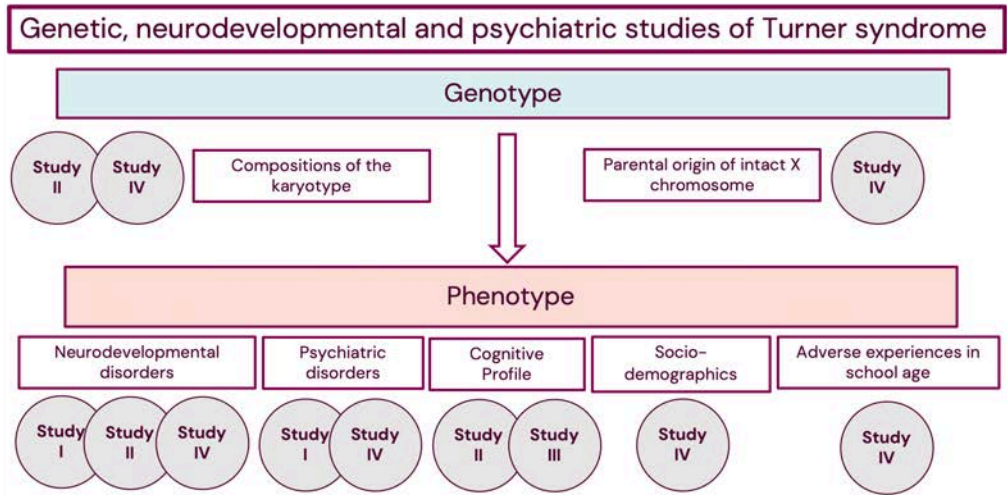


Figure 1. Overview of the relationship of the genotype and aspects of the phenotype that are covered in this thesis.

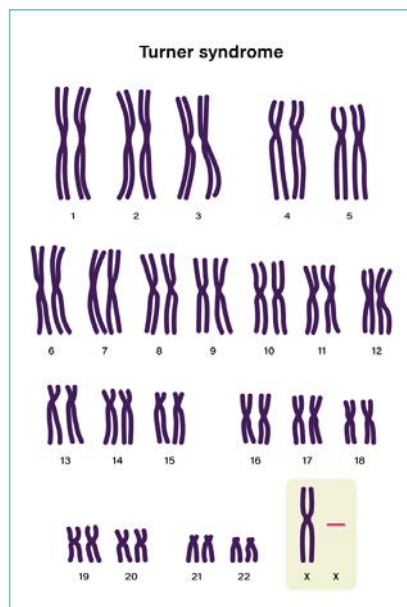
2 Thesis at a glance

Study	Research questions	Methods	Results	Conclusions
I	What is the prevalence of neurodevelopmental and psychiatric disorders in TS?	A retrospective cohort study 1392 females with TS diagnose were identified in the Swedish NPR and 1:100 age- and county of birth-matched female controls from the general population. Associations between TS and diagnoses of neurodevelopmental and/or psychiatric disorders were calculated using conditional logistic regression and presented as estimated risk compared with matched controls.	Individuals with TS had a higher likelihood of having a neurodevelopmental and/ or psychiatric disorder compared with controls. The results showed an eightfold increased risk of ID, and a fourfold increased risk of ASD compared to controls. In addition, females with TS had twice the risk of a diagnosis of schizophrenia.	Females with TS have a higher likelihood of receiving a diagnosis of neurodevelopmental and/ or psychiatric disorders. Cognitive assessment from an early age, and neurodevelopmental and psychiatric evaluations should be done continuously as part of regular care of individuals with TS.
II	Is TS in adulthood associated with elevated symptoms of ADHD and autism spectrum disorder? Is the previously described uneven cognitive profile, characterized by a relative strength in verbal compared to non-verbal functions, clinically significant? Is the degree of verbal > non-verbal IQ-split associated with symptoms of ADHD and ASD?	Cross-sectional study, including 30 adult Swedish women with TS. Psychological tests and standardized questionnaires were used to assess cognitive profile and symptoms of ADHD and ASD. Both frequentist and Bayesian statistics were applied.	Cognitive profile was characterized by a verbal > non-verbal split, exceeding cut-off for clinical significant split in 77% of the participants. No association between the verbal > non-verbal split and symptoms of ADHD/ASD was found. ASRS scores showed dominating challenges in inattention compared to in hyperactivity/ impulsivity in 77% of the participants.	The adult women with TS had a clinical significant verbal > non-verbal split in 77% of the 30 women. Impairments in certain integrative executive functions were found. It is urgent to further investigate the clinical impact of an uneven cognitive profile in women with TS.
III	Is TS associated with an altered effect of social feedback on reinforcement learning?	Cross-sectional case-control study. Experimental designed online study, 35 adult women with TS and 37 matched controls performed a probabilistic task requiring learning through social and non-social feedback. Data were analyzed using computational modelling and analyses of choice behavior.	In the experimental reinforcement learning task social feedback had an effect of more explorative choice behavior in the control group, and lead to reduced learning compared to non-social feedback. No effects of social feedback on learning were found in the TS sample.	No effects of social feedback on learning compared to the controls were found in the group of TS individuals suggesting that women with TS may be less sensitive to social influences on reinforcement learning than the general population.
IV	Is the phenotype in TS affected by the parental origin of the X-chromosome? If so, how does the phenotype differ due to maternal or paternal origin of the X-chromosome?	Parental origin of the remaining X-chromosome was identified (X _m or X _p) in 80 adult women. X _m and X _p -groups were compared with karyotype, self-reported relationship status, educational attainment, employment rate, and experiences of academic and social challenges during school-age. Diagnoses of neurodevelopmental and psychiatric disorders were extracted from medical records.	No significant differences were identified based on X _m or X _p , or karyotype. Compared to the general population, descriptive analyses, independent of parental origin of the X in TS seemed to have higher numbers of depression, anxiety and increased self-reported academic and social difficulties during school age. Occupational and educational status was the same as females in general population in Sweden.	Women with TS appear to be at elevated risk for developing depression and anxiety disorders. Interestingly, our results indicate that these risks are independent of karyotype and origin of the retained X chromosome.

3 Literature review

3.1 Background

Turner Syndrome (TS) is a genetic condition in females with a partial or complete loss of one of the two sex chromosomes occurring in about 1:1700–2000 female births (12, 13). This background section gives an overview of the genotype and etiology, as well as the current knowledge regarding challenges associated with TS from neurodevelopmental, psychiatric, cognitive, and psychosocial perspectives.



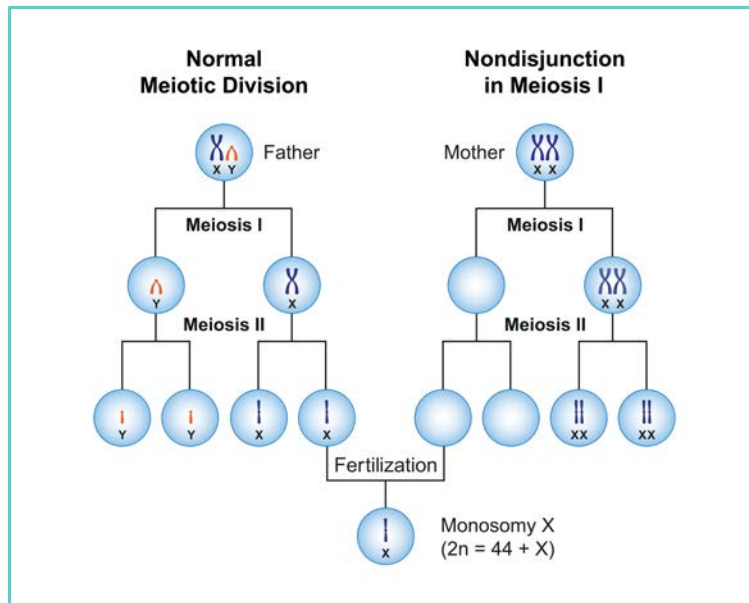
Published with permission. (2023). Human karyotype of Turner syndrome

Figure 2. Karyotype of Turner syndrome (45,X).

3.2 Karyotype

The karyotype monosomy 45,X (Figure 2) is the most common karyotype in TS (40%–50% of cases), and mosaicism 45,X/46,XX is the most common mosaicism in TS (15%–25% of cases) (1, 13, 14). Other forms of mosaicism include 45,X/46,XY (4%–12% cases), or 45X along with one or multiple cell lines containing additional combinations of X chromosomes. Karyotypes with structural variations of the X chromosome include deletions, isochromosomes, or ring chromosomes leading to a loss of its genetic material that impacts either the long or short arm of the X chromosome to various extents (24%–30%) (1, 13, 14). TS is most often caused by

a failure in the separation of the sex chromosomes during the formation of the egg or sperm (Figure 3) (15).



Published with permission (2023). Scientific Designing of Nondisjunction in Monosomy X (Turner Syndrome)

Figure 3. Nondisjunction in maternal meiosis II, causing maternal loss of X the X chromosome.

3.3 Why is it important to have two sex chromosomes?

The two sex chromosomes, X and Y, control development into the biological sexes male (46,XY) or female (46,XX). The Y chromosome is important in determining male sex (XY), but cannot, like the X-chromosome, contribute the genetic information needed for progression into viable embryos. Thus, embryonic eggs without the genetic information from the X chromosome (45,Y) do not survive (15–17).

In females with a 46,XX karyotype, it is necessary to suppress the activity of genes on one of the two X chromosomes in every cell to maintain balanced gene expression. This silencing mechanism, called X-chromosome inactivation, is caused by a series of epigenetic events (see Figure 4) (9). Failure in inactivation could lead to harmful overproduction of proteins, as X-linked genes would be expressed at twice the normal level. Thus, the random inactivation between X chromosomes of parental origin (X_m or X_p) during early development persists in all cells throughout an individual's life (18, 19).

However, the chemically silenced X chromosome still exhibits some gene activity after inactivation due to “escape genes”, consequently requiring two functional alleles for proper function (20, 21). Furthermore, epigenetic modifications, such as DNA methylation, can mark genes for differential expression based on their parental origin, a phenomenon known as genomic imprinting (21, 22).

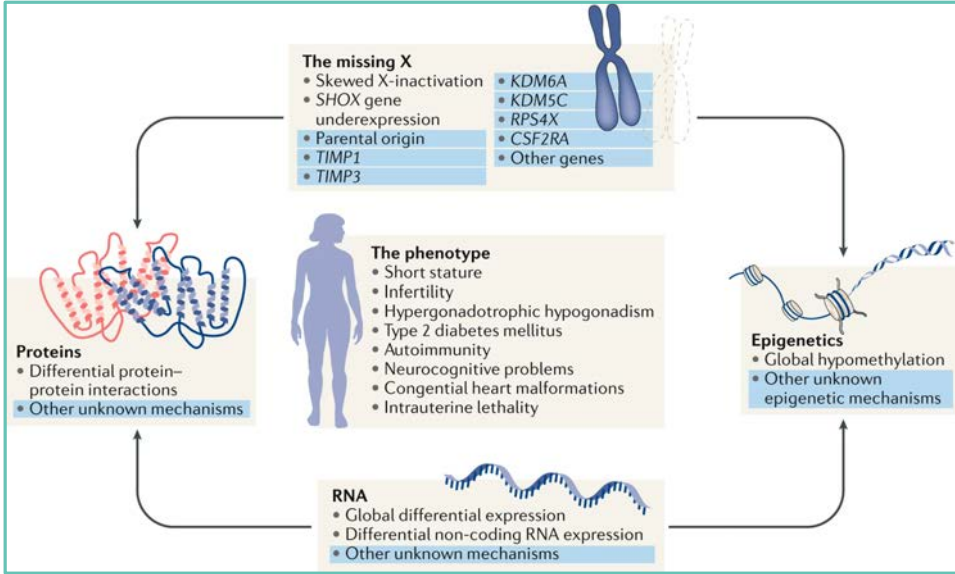


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Figure 4. Figure presented in Gravholt et al. (2019): "The figure depicts the current understanding of the genomics of Turner syndrome, incorporating recent genomic results. In addition, disorders that characterize the phenotype of Turner syndrome are listed. Arrows depict possible, but not proven, pathways. Genes and mechanisms with a possible, but not proven, involvement in the pathogenesis of Turner syndrome are highlighted in blue"(9).

The pseudoautosomal regions (PAR1 and PAR2) are short regions of sequence homology between the sex chromosomes and found at the short arm tips (PAR1) and long arms tip (PAR2) of both X and Y chromosomes respectively. The *SHOX* (short stature homeobox-containing) gene is located in PAR 1 and both females and males normally have two functional copies of the gene located in the PAR regions in each cell (23).

Due to the continued activity of some genes, such as *SHOX* in the inactivated X chromosome in 46,XX karyotype, the loss of X chromosome material affects gene expression in TS. The *SHOX* gene is sensitive to haploinsufficiency and thus, as individuals with TS only have one PAR1 region and one copy of the *SHOX* gene, they often present with short stature. In contrast, males with sex chromosome aneuploidies consisting of three sex chromosomes, such as Klinefelter’s syndrome

(47,XXY), express increased levels of SHOX and often present taller than their estimated final length (24, 25). Furthermore, it has been suggested that other genes in the PAR regions regulate aspects of the neuroanatomical and cognitive profile in TS, possibly explaining the postulated deviating cognitive profile in individuals with TS (26, 27).

3.4 Ovarian dysfunction and hormonal influence

As mentioned previously, one of the most common features of women with TS are ovarian dysfunction. The embryonic gonadal dysgenesis causes an ovarian insufficiency and decreased production of estrogen, progesterone, testosterone and inhibin, starting in fetal development and through the lifespan (4, 28). A majority of individuals with TS present with primary amenorrhea, and only 10–15% have a spontaneous menarche. The ovarian phenotype seems to be most severe in women with non-mosaic 45,X karyotype and milder in 45,X/46,XX mosaicism (28). The loss or absence of ovarian function results in a hypoestrogenic state, a hypergonadotropic hypogonadism (29). Hormone replacement therapy tries to mimic normal pace of physical and social development while minimizing risks. In girls with TS, treatment with exogenous estradiol is part of the clinical guidelines, introduced to time puberty typically around the age of 11–12 years (28, 29).

The hormonal influence of the developing human brain is well known and estrogen has multiple effects on brain function (30). Previous research implicates that estrogen modulates neurotransmitter function as well as brain aging and cognitive functions such as memory. In line with this, estrogen might also be involved in the etiology of neurodevelopmental disorders (31). For example, the fetal exposure of atypical levels of sex steroids has been suggested as a possible causative factor in ASD in the general population (32). Further, levels and function of estrogen in relation to mood-depressive disorders with several different mechanisms involved have been discussed, but not yet fully understood. However, overall, the imbalance in levels of hormones in TS is suggested as a vulnerability for depressive disorder (33).

The hypothesis of a causal relationship of hormones and ASD is particularly interesting to study in TS, since the imbalance in hormonal exposure and an increased risk of social impairments in TS may provide potential insights into causation (34). However, as discussed in a study by May et al. 2021, it is complicated to reveal the causal effects between genetics, hormones and risk factors in the fetal environment since low birth weight and premature birth,

common in TS, is in and of itself related to ASD (34). Levels and function of estrogen in relation to mood-depressive disorders has been discussed, with several different mechanisms involved, but is not yet fully understood. Overall, the imbalance in hormone levels in TS is suggested predisposing individuals with TS to depressive disorders (33).

This thesis will focus on the TS phenotype related to neurodevelopmental and psychiatric disorders, as well as cognitive characteristics and psychosocial challenges (Figure 5).

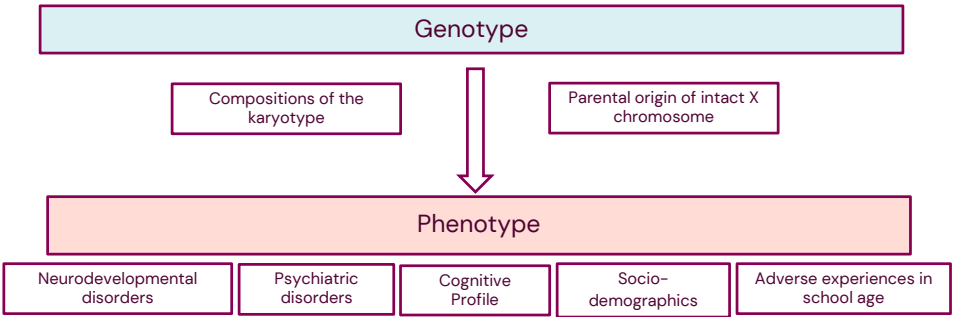


Figure 5. Overview of the relationship of the genotype and aspects of the phenotype that are in focus in this thesis.

3.5 Neurodevelopmental disorders in Turner syndrome

Attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is characterized by daily life challenges arising from inattention, hyperactivity, and impulsivity (35). There is an increased likelihood of ADHD in individuals with TS with studies indicating a prevalence up to 25 % (36–38), as compared with 2% of females in the general population (39–41). Unlike children and teenagers from the general population who typically exhibit symptoms from both the ADHD domains, children and teenagers with TS have been reported to show more pronounced symptoms in the hyperactivity/impulsivity domain (36, 37). However, data regarding whether this pattern persists into adulthood for women with TS is limited (42).

Autism spectrum disorder

Autism spectrum disorder (ASD) is characterized by challenges in social communication and interaction and with restricted and repetitive behaviors. The overlap, and distinction between social challenges and ASD in individuals with TS

has been in focus of discussion (43–45). However, several studies show that the social impairments in TS meet the diagnostic criteria for ASD (45–47). One of the earliest studies, by Creswell & Skuse (1999), reported a prevalence of 3 % ASD in females with TS, which is twice the estimated incidence in the general population (45).

Psychiatric disorders

The existing literature suggest an increased risk of depression and anxiety in individuals with TS, but psychiatric disorders are in general not extensively studied, and results vary (33, 48–51). In a literature review of depressive disorders, Morris et al. (2020) showed that there was an elevated risk for depressive disorder in individuals with TS compared to the general population, especially in adult women with an incidence between 36% and 65.2% (33). In a recently published retrospective medical record review of 631 individuals with TS, Kramer et al. (2023) reported a prevalence of anxiety at 17.4% and depression at 6.7% (50). Furthermore, Alexandrou et al. (2022) found elevated anxiety scores in 65% of 92 participants with TS (49).

Cognition

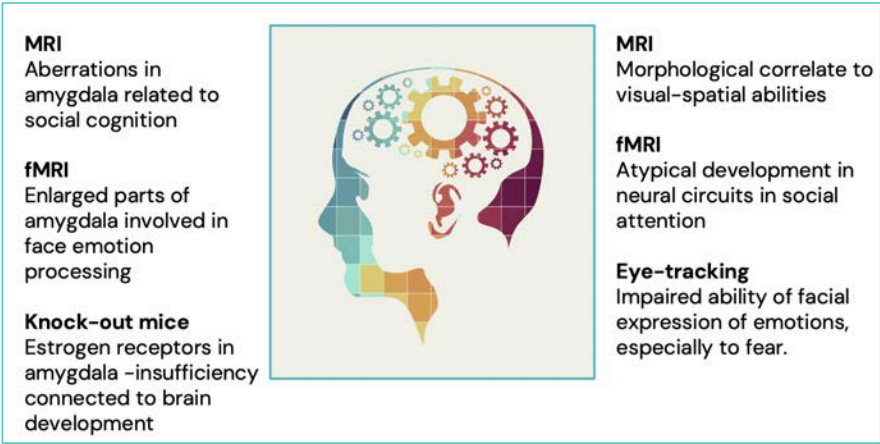
It is well-documented that most girls and women with TS have an intelligence quotient (IQ) within the normal range with a cognitive profile often characterized by relative strengths in the verbal domains, and weakness in the visual-spatial domain (52–54). However, the clinical impact of the uneven profile in functioning of individuals with TS is not clear. In addition, challenges with attentional regulation and executive function, particularly cognitive flexibility, are reported in individuals with TS (55). Still, there are only a few studies investigating executive impairments as well as ADHD in adult women with TS (47, 48).

Psychosocial and challenges in social attention

Girls and women with TS are often described to face social challenges, and compared to their peers, individuals with TS typically have fewer social contacts, fewer romantic relationships, and engage in fewer social activities throughout their lives (46, 56–59).

There have been several attempts to find consensus and understanding of the etiology and content of these social challenges (11, 43, 52, 54, 60, 61). Individuals with TS are suggested to have (as do individuals with ASD) deficiencies in visually

interpreting facial emotional expressions such as fear (62–64). Perceiving emotional expressions is an important aspect of social interaction and is therefore suggested to be a contributing factor in the social challenges described in TS (65). Another aspect of perceiving facial expressions is the role as a powerful reinforcer is in social learning (66), but studies in individuals with TS and social reinforcement learning are lacking. However, a social desire is reported in studies of individuals with TS that has been compared to tendencies of reduced social motivation to engage with peers in individuals with ASD (43, 60).



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Figure 6. Examples of findings in neuro imaging and eye-tracking.

3.6 Neuroimaging

Magnetic resonance imaging (MRI) studies of the brain in participants with TS have shown decreased grey matter volume in parietal and postcentral gyri, suggesting a morphological correlate to some aspects of the cognitive profile as the impaired visual-spatial abilities, as exemplified in Figure 6 (67–69). Supporting this suggestion, studies using functional magnetic resonance imaging (fMRI) have shown atypical development in neural circuits important to spatiotemporal abilities and attention in individuals with TS (54). In addition, there are findings in fMRI of aberrations in amygdala, suggested to relate to social cognition such as social attention and face emotion processing of fear (62, 70), facial recognition, and perception of gaze (71).

3.7 Eye-tracking

The eye movements reflect what the individual pay attention to and how. Looking and at other people's faces and perceiving information from gaze and emotional expression of the face of others is a high priority for further cortical processing (72). Atypical eye movement patterns in individuals with TS related to facial recognition and ability to recognize the facial expression, especially fear, has been reported in eye-tracking studies (63, 64).

3.8 Associations between genotype and themes of phenotype

Understanding the phenotypic expressions in TS requires the consideration of multiple factors. There is significant variation in the phenotype among individuals with the same TS genotype, and the underlying genetic mechanisms behind this variation are not yet fully understood. The literature suggests various factors that might contribute to the to the broad range of manifestations and variable expressivity in TS, such as the different karyotypes (73), the parental origin of the retained X chromosome (61) and considerations including genomic and epigenetic changes caused by genomic imbalance (74).

3.9 Karyotype—Phenotype

While individuals with the same karyotype can have varied manifestations, a correlation between certain karyotypes and manifestations or level of expression has been indicated. Among individuals with TS and the mosaic karyotype 45,X/46,XX, a milder phenotype has been described in terms of cognitive abilities (73, 75, 76). In contrast, the karyotype with a ring-X chromosome is the only karyotype that shows a significantly higher risk of intellectual disability (77, 78). However, it has been reported that individuals with monosomy 45,X have a higher level of discrepancy between the domains of the cognitive profile, as well as a lower average total IQ compared to mosaicism 45,X/46,XX (53, 76), but a meta-analysis by Mauger et al. (2018) reported conflicting findings that no significant differences were identified between those with mosaicism and monosomy (55).

3.10 Parental origin of the X chromosome

Previous studies have showed that the retained fully functioning X chromosome in TS is of maternal origin (X_m) in approximately 70% and of paternal origin (X_p) in approximately 30% (79, 80).

The effect of the X chromosome's parental origin has been an area of great research interest for both the physical manifestations and the cognitive phenotype in TS. Skuse et al. (1997) found that individuals with Xp showed better verbal skills and fewer social-communication challenges than those with Xm (61). Further, Bishop et al. (2000) observed superior visuospatial abilities in Xp (81) and Loesch et al. (2005) reported lower verbal IQ in both women and girls with Xp compared to Xm (82). Hall et al. (2022) further reported that girls with Xm displayed more gaze avoidance in social situations than those with Xp (83). In addition, several studies reported differences between women with Xm and Xp in neuroimaging such as smaller right temporal gyri found in Xm than in Xp (84). Differences in cortical thickness in temporal and frontal cortical areas were also reported in prepubescent girls with Xm and Xp respectively (85).

However, there are also several studies that have shown contradictory results; namely, that parental origin of the X chromosome does not affect the phenotype in TS. Russell et al. (2006) found no ADHD or IQ differences among 50 girls with TS regardless of whether their X chromosome was of maternal or paternal origin (37). Lepage et al. (2012) also reported that no significant differences in cognitive function and symptoms of ASD or ADHD between Xm and Xp in prepubescent children was found (86). In addition, Gould (2013) compared education levels, marital status, and employment rates between women with Xm and Xp, finding no notable differences (80).

Overall, the evidence related to differences between Xm and Xp origin in cognitive, neurodevelopmental, or psychiatric expression remains inconclusive. In addition, the majority of studies have been conducted in children or adolescents with monosomy 45,X. Additional research is essential to deepen our understanding of the complex interplay between the X chromosome's parental origin and phenotypical associations in TS.

3.11 Knowledge gap

The large interindividual differences and the number of possible expressions of the phenotype in individuals with TS are not clearly understood. To effectively develop or utilize existing therapeutic approaches for challenges linked to TS, it's crucial to identify similarities between conditions like TS and other disorders, while also recognizing their distinct differences. For instance, the autistic phenotype is a continuum in which individuals, perhaps especially in clinical conditions with an atypical cognitive profile, can exhibit numerous autistic traits without necessarily

meeting the full criteria for a diagnosis of ASD (87). Exploring the social challenges associated with TS by examine outcomes of daily life in TS, as well as conducting experiments to uncover potential insights in underlying mechanisms, would be advantageous.

Furthermore, there is a notable knowledge gap when it comes to studies focusing on adult women with TS. The limited number of studies investigating aspects of cognitive, neurodevelopmental and psychiatric challenges in adulthood may delay clinicians' ability to find and treat these conditions and hinder a deeper understanding of the variations in phenotypic expression in the maturing brain of women with TS.

Finally, the impact of parental origin of the X chromosome in relation to phenotype is still unclear. The literature shows conflicting results, but the majority of studies examine children or adolescents and only with karyotype 45,X. Studies of parental origin of the X chromosome including all karyotypes are scarce; therefore, further insights into whether the distribution or impact of X_m and X_p differ between karyotypes are needed.

4 Research aims

Overall aim

The overarching aim of this thesis was to examine the cognitive profile, psychosocial outcomes, and mental health in females diagnosed with Turner syndrome.

Research questions

1. What is the prevalence of neurodevelopmental and psychiatric disorders in TS?
2. Is TS in adulthood associated with elevated symptoms of ADHD and autism spectrum disorder?
3. Is the previously described uneven cognitive profile, characterized by a relative strength in verbal compared to non-verbal functions, clinically significant?
4. Is the degree of verbal > non-verbal IQ-split associated with symptoms of ADHD and ASD?
5. Is TS associated with an altered effect of social feedback on reinforcement learning?
6. How is the distribution of the parental origin of the X-chromosome in women with TS?
7. Is the phenotype in Turner syndrome affected by the parental origin of the retained X-chromosome? If so, how does the phenotype differ due to the maternal or paternal origin of the X-chromosome?

5 Materials and methods

Table 1 Overview of research question materials and methods in the studies.

Study	Research questions	Design	Study sample	TS diagnosis and genetic analysis	Outcome measures	Statistical analysis
I	What is the prevalence of neurodevelopmental and psychiatric disorders in TS?	Population-based retrospective cohort study	All females diagnosed with TS in Sweden until 2013 (n =1392) 1:100 age- and sex-matched controls (n =139,200)	Diagnosis of TS extracted from the National Patient Register	Neurodevelopmental and psychiatric diagnoses registered in the Swedish National Patient Register	Conditional logistic regression
II	Is TS in adulthood associated with elevated symptoms of ADHD and autism spectrum disorder? Is the previously described uneven cognitive profile, characterized by a relative strength in verbal compared to non-verbal functions, clinically significant? Is the degree of verbal > non-verbal IQ-split associated with symptoms of ADHD and ASD?	Cross-sectional study	Adult women with a diagnosis of TS (n =30) Participants compared to published norm data	Diagnosis of TS extracted from medical records Karyotypes extracted from LIS and medical records	Standardized cognitive testing (WAIS-IV) and self-ratings of symptoms of ASD (AQ) and ADHD (ASRS).	One-sample t-tests Paired t-tests Linear correlations (Pearson correlation coefficient)
III	Is TS associated with an altered effect of social feedback on reinforcement learning?	Cross-sectional case-control study Experimental manipulation of feedback type in learning task	Adult women with TS (n =35) Control group of adult women without known genetic disorders (n =37)	Diagnosis of TS self-reported (n =35) and later confirmed in medical records (n =30/35), Karyotypes extracted from LIS and medical records	Choice behavior in reinforcing learning tasks	Computational modelling Linear mixed effects models Wilcoxon tests
IV	Is the phenotype in TS affected by the parental origin of the X-chromosome? If so, how does the phenotype differ due to the maternal or paternal origin of the X-chromosome?	Cross-sectional retrospective study	Adult women with TS syndrome (n =80) of which Xm =57 and Xp =23	Molecular genetic analysis (QF-PCR) performed to confirm a diagnosis of TS and identify the origin of the X-chromosome and confirm a diagnosis of TS Karyotypes extracted from LIS and medical records	Sociodemographic variables and school-age experiences assessed with a custom self-report instrument Diagnoses of neurodevelopmental and psychiatric disorders extracted from medical records.	Mann-Whitney U-tests χ^2 -tests Binomial tests

5.1 Overview of methods in Study I-IV

In **Study I-V**, the study design, data collection, and statistical analyses differ in various respects (see Table 1 for overview). However, the four studies share a focus on examining aspects of cognitive and psychosocial characteristics as well as manifestations of neurodevelopmental and psychiatric disorders in individuals with Turner syndrome.

Study design

Study I is a register, population-based retrospective cohort study, **Study II** and **III** are cross-sectional, and **Study IV** is a cross-sectional study with retrospective outcome data. In **Study I** and **III**, individuals with TS were compared to control groups, whereas **Study II** compared participants to published normative data for the included measures. **Study IV** compared women with TS and a maternally retained X-chromosome compared to those with a paternally retained X-chromosome. An overview of the methods used in the studies can be seen in Table 2.

Outcome measures

Where **Study I** and parts of **Study IV** have collected diagnoses of disorders, **Study II** focuses on cognitive and neurodevelopmental measurements. In **Study III**, an experimental task allowed us to compare the effects of social compared to non-social feedback on learning.

Table 2. Methods used in the thesis.

	Study I	Study II	Study III	Study IV
Medical records review				X
Laboratory information systems		X	X	X
Cognitive testing		X	X	
Self-reported symptom ratings		X		
Self-reported socio-demographics				X
Self-reported school experiences				X
DNA analysis				X
Cognitive experiment			X	
Diagnoses identified in national patient registers	X			

Statistical analyses

The aim of **Study I** was to estimate the degree of association between register-based TS diagnoses and diagnoses of psychiatric and neurodevelopmental disorders. To address this aim, conditional logistic regression analyses were used to compare the likelihood of having diagnoses of psychiatric and neurodevelopmental disorders between participants with TS and controls presented as estimated risks (odds ratio, OR, 95% confidence interval, CI).

In **Study II** and **III**, we estimated group differences and bivariate linear relationships between variables in the population. Thus, parametric statistical tests (Pearson correlations, t-tests, linear mixed effects models) were used when assumptions for these were fulfilled. When the assumptions of normal distribution (**Study II–III**) were not fulfilled or if data were categorical rather than continuous (**Study IV**), data were instead analyzed using non-parametric Kruskal-Wallis and Mann Whitney tests for continuous data, and χ^2 tests for categorical data.

In addition to these methods, **Study III** extended the analysis by using computational modeling, a method in which mathematical models are fitted to the directly observable data to extract latent variables, helping us identify potential insights about the underlying cognitive mechanisms.

5.2 Study I

“Neurodevelopmental and psychiatric disorders in females with Turner syndrome: a population-based study”

Research question

1. What is the prevalence of neurodevelopmental and psychiatric disorders in TS?

Study design

Swedish national registers were used to compare the risk of neurodevelopmental and psychiatric disorders in TS with controls from the general population. The design of the study was a population-based retrospective cohort study (see Figure 7).

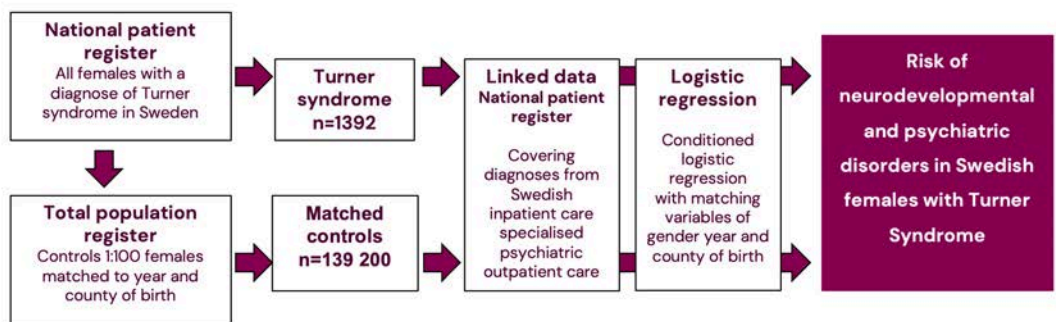


Figure 7. Overview of study design in Study I

Outcome measures

Outcome measures were defined as a diagnosis of neurodevelopmental and psychiatric disorders within ICD-8 codes 290–315, ICD-9 codes 290–319, and ICD-10 codes F10–F99 in the the National Patient Register (NPR).

Data collection—National registers

In Sweden, every citizen receives a unique personal identification number that is used in all registers and official records and enables information from different registers to be linked together. Linkage between population-based registers for

research purposes is made possible through Statistics Sweden, which has generated a key that converts the personal identification number into a unique ID number resulting in pseudonymized, de-identified data for each individual. The key is not available to researchers in order to keep individuals' identities confidential (88). Each individual with a TS diagnosis was identified from the NPR and matched with 100 female controls—females from the general population matched by county and date of birth from the the Total Population Register (TPR) that records data, including birth, death, name change, and migration status updated by the Swedish Tax Agency (89). NPRs coverage of collecting diagnoses have changed over the last few decades (see Figure 8). To validate the diagnoses in NPR, studies have been comparing the register with medical records, with a positive predictive value of 85%–95% for most diagnoses (90).

The coverage of National Patient Register

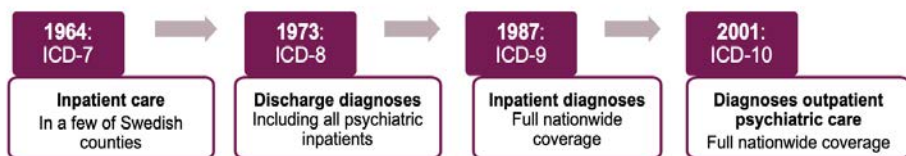


Figure 8. Coverage of National Patient Register

Statistical analysis

Comparisons of the associations with each outcome measurement (i.e., diagnoses of psychiatric and neurodevelopmental disorders) between the matched controls and individuals with a diagnosis of TS were calculated with conditional logistic regression and presented as estimated odds ratios with 95% confidence intervals.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was received by the Regional Ethics Committee of Stockholm, Sweden 2013/862–31/5.

5.3 Study II

"Cognitive profile in adult women with Turner syndrome: IQ split and associations with ADHD and ASD"

Research questions

1. Is TS in adulthood associated with elevated symptoms of ADHD and autism spectrum disorder?
2. Is the previously described uneven cognitive profile, characterized by a relative strength in verbal compared to non-verbal functions, clinically significant?
3. Is the degree of verbal > non-verbal IQ-split associated with symptoms of ADHD and ASD?

Study design

In this cross-sectional study, standardized psychological tests and questionnaires were administrated in thirty adult women with TS syndrome. Within-subject comparisons and comparisons to published population norms were done (Figure 9).

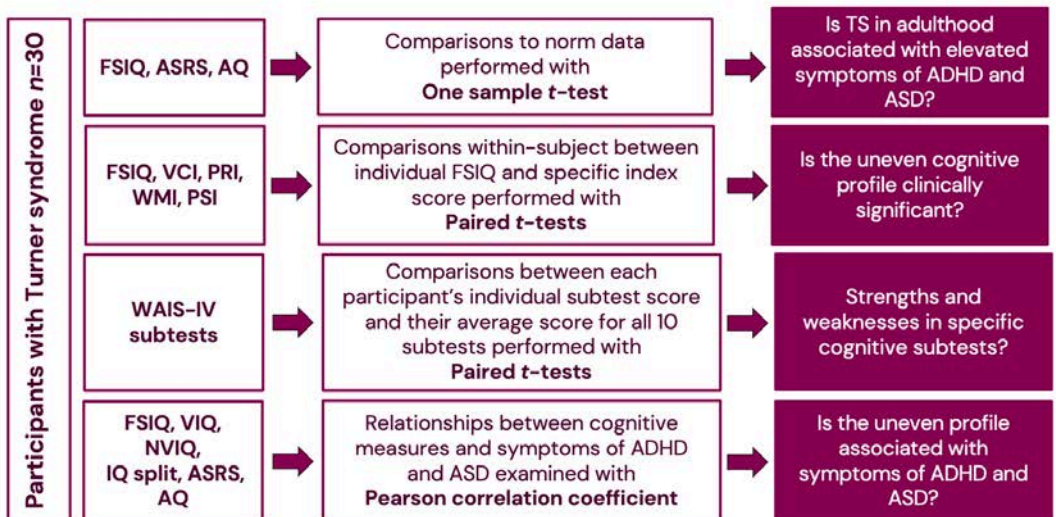


Figure 9. Overview of study design in study II

Outcome measures

The variables of interest included test results from The Swedish version of 4th edition Wechsler Adult Intelligence Scale (WAIS), (see Table 3), scores on the self-reported symptoms in the Adult ADHD Self-reported Rating Scale questionnaire (ASRS), (see Figure 10), and scores on the autism spectrum quotient self-screening instrument for adults (AQ), (see Figure 11).

Data collection

The inclusion criteria were a confirmed genetic diagnosis of TS, be older than 18 years, and be fluent in Swedish. Exclusion criteria were acquired brain injuries, such as dementia, stroke, or brain tumours. Recruitment was conducted through Women’s Health Research Unit at Karolinska University Hospital. The assessments were performed by one clinical psychologist and two trained psychology students at Karolinska University Hospital. Participants completed the ASRS and AQ questionnaires either at home or during their visit. Data of the karyotypes of the participants were obtained from their medical records and the laboratory information systems (LIS).

Table 3. Structure of the Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV).

Full-scale intelligence quotient (FSIQ)	Index score	Subtest
	Verbal Comprehension (VCI)	Similarities
		Vocabulary
		Information
	Perceptual Reasoning (PRI)	Block Design
		Matrix Reasoning
		Visual Puzzles
	Working Memory (WMI)	Digit Span
		Arithmetic
	Processing Speed (PSI)	Symbol Search
		Coding

WAIS-IV was used to assess general intellectual ability and cognitive profiles (91). Index scales and FSIQ are normally distributed with a mean of 100 and standard deviation (SD) of 15 in the norm group and the four index scales consist of different core and additional subtests (91). The 10 core subtests were administered in the current study (see Table 3). The following cognitive measures were used in the analyses: full-scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ),

non-verbal intelligence quotient (NVIQ), and IQ split VIQ-NVIQ. Verbal comprehension index scores (VCI) in WAIS-IV, is a measure of verbal reasoning and comprehension, and were used as an index of VIQ. Perceptual reasoning index scores (PRI) in WAIS-IV, measure visuospatial abilities and non-verbal reasoning, and were used as an index of NVIQ. IQ split was defined as VIQ-NVIQ relatively stronger VCI in comparison to PRI. According to the Wechsler manual, a clinically significant discrepancy between the different index scales is defined as an absolute difference between two scales occurring in $\leq 15\%$ of the normative sample (91).

Self-reported symptoms in Adult ADHD Self-reported Rating Scale (ASRS)

The ASRS v.1.1 was used for the assessment of ADHD symptomatology (Figure 10). The scale is the World Health Organization’s 18-item Symptom Checklist of adult ADHD and was created as a screening tool for current ADHD symptoms. The total 18-item scale was used as a measure of continuous ADHD symptoms in correlational analyses and as a categorical measure in comparison to norm data. The norm data were established from a population-based study of >12,000 typical American adult women (92). Symptoms are rated on a Likert scale; 1–5 (never, rarely, sometimes, often, or very often), and the checklist is divided into two parts. Part A consists of 6 questions and Part B of 12 questions. Part A (the shorter ASRS self-reported screener) has standardized cut-off scores of ≥ 4 out of 6, Part B provides supplementary information on symptoms and makes it possible to compare the two domains of symptoms; inattention and hyperactivity/impulsivity (93).

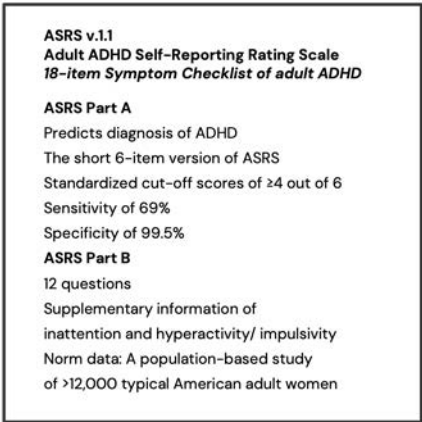


Figure 10 Self-reported symptoms in Adult ADHD Self-reported Rating Scale

Total AQ scores were used to distinguish individuals above the screening criteria cut-off and also used as a quantitative measure of autistic symptoms in comparison to norm data. The norm data was based on 1378 typically developed adult women reported in a systematic review 2015 (94). AQ questionnaire is a self-screening instrument to measure autistic traits in individuals with normal intelligence (Figure 11). The scale consists of 50 items and the results are given as a continuum with scores in the range of 0–50 (95). A cut-off score of 26 on the total scale has proven to be useful as a screening measure for ASD, and was used in the present study (96).

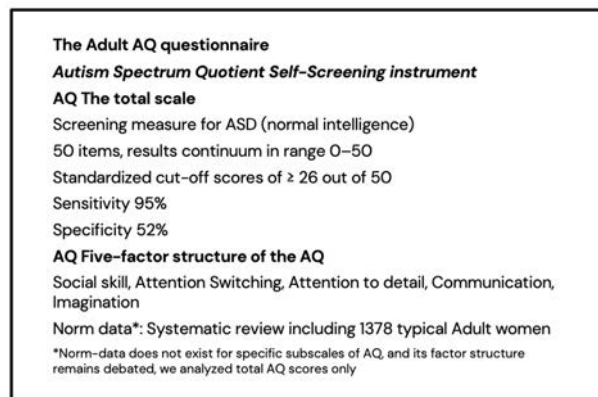


Figure 11. Autism spectrum quotient self-screening instrument for adults

Statistical analyses

As described in Figure 9, comparisons with norm data for the total scores of FSIQ, ASRS, and AQ were performed with one-sample t-tests. Cohen's d was used as a measure of effect size. To examine strengths and weaknesses in the individual cognitive profile, on index and subtest levels respectively, paired sample t-test was used to test statistically significant differences between FSIQ and index/subtest scores. Associations between quantitative measures of s ADHD and ASD symptoms and cognitive measures were examined using Pearson's correlation coefficient. The significance level was set to 5% for all analyses ($\alpha = 0.05$) and two-tailed p-values are reported. Significance thresholds were adjusted for multiple comparisons using the Bonferroni correction.

Initial analyses showed that scores on the PSI index and on the WAIS-IV symbol search subtest were not normally distributed, nor were the bivariate residuals in the correlational analyses in the correlations between ASRS and PRI and between AQ and PRI. Deviations from the normal distributions were not found on any of the other variables. Using non-parametric Wilcoxon tests for significant differences between FSIQ and PSI/Symbol Search and Spearman correlations for the associations between ASRS-PRI and between AQ- PCI, did not alter the significance of the results, hence parametric tests were consistently applied. Data were analyzed using Bayesian statistics in addition to traditional frequentist statistics. Whereas traditional statistics only determine whether the null hypothesis can be rejected, Bayesian statistics compares the probability of the starting assumption, (i.e., the null hypothesis testing) and the alternative hypothesis. Thus, Bayesian statistics can quantify the relative probability of the null and alternative hypotheses, and therefore also generate proof for the null hypothesis (97). As the same statistical assumptions of data distribution apply to Bayesian and frequentist statistics (e.g. normally distributed residuals), no additional assumption checks were made.

Power analysis

A power analysis conducted in the R library pwr (98) showed that the study had 80% power to detect correlations at $r = .49$ or above and differences from known population means (i.e., effects in one-sample t-tests) at $d = 0.52$.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was received by the Regional Ethics Committee of Stockholm, Sweden (dnr 2014/91, 2018/431-32).

5.4 Study III

“Reduced effects of social feedback on learning in Turner syndrome”

Research question

1. Is TS associated with an altered effect of social feedback on reinforcement learning?

Study design

In this cross-sectional case-control study results of choice behavior and learning were compared between women with TS and a control group due to social and non-social feedback in an experimental reinforcement learning task.

The reinforcement learning task (described in Figure 12) was adapted from Kleberg et al. (2023) (99). Two versions of the tasks, with social and respectively non-social conditions were completed by the participants using either a tablet or computer. The two versions presented a choice between two stimuli across 75 trials, with a probability of winning 2/3 and 1/3 a point, respectively. Therefore, if a hypothetical participant would consistently choose the correct stimulus in all 75 trials, the participant would succeed in winning a point in approximately two thirds of the attempts. For clarity, this ‘most rewarding choice in the long run’ is hereafter referred to as the ‘correct choice’ but would nevertheless always win a point. Mastering the task therefore requires the participant to learn through exploration which action is most likely to result in a favorable outcome.

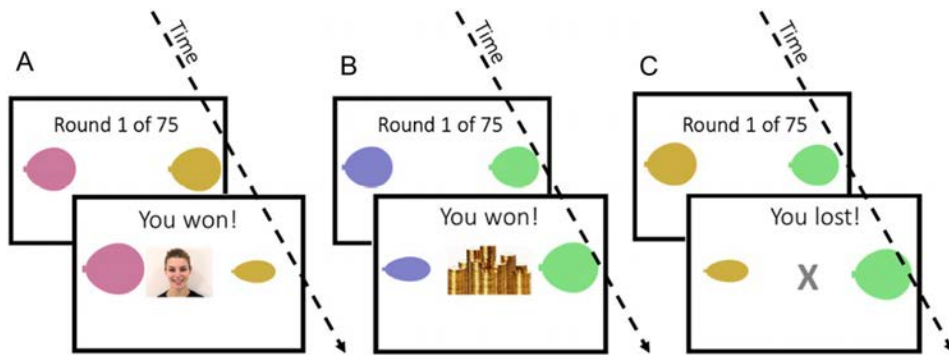


Figure and figure legend citation published with permission from Scientific Reports (100).

Figure 12. “Experimental design. In counterbalanced order, participants completed 75 trials in each condition rounds. Choosing the correct option was followed by receiving (A) social feedback (animation of a smiling face, social condition) or (B) non-social feedback (animation of a stack of gold coins, non-social feedback). Incorrect choices, in both condition rounds (A and B), were followed by an animation of the letter ‘X’ moving towards the participant, (C). In both conditions, the reward probabilities of the stimuli were 2/3 and 1/3 respectively. Stimulus color and position of the better stimulus (left/right) were counterbalanced between participants and conditions.”

Outcome measures

The different choice behavior outcomes were measured by the proportion of trials where the participant’s choice was more likely to be awarded a winning point (% correct), where participants switched from the previous choice (% volatility), and the proportion of switches following wins (% switch-win) and losses (% switch-lose). While the percentage of correct choices reflects task performance, the percent volatility, percent switch-win, and percent switch-lose provide measurements of strategy and cognitive processes involved in solving the task. The outcomes of underlying mechanisms analyzed in behavioral data with computational modelling (see statistical methods) were presented as learning rate (α parameter value) and exploratory behavior (β parameter value).

Data collection

Participants with TS, age >15 years ($n = 35$) were recruited by Karolinska University Hospital and by advertising through a patient organization for individuals with TS. The control group of adult women without known genetic disorders ($n = 37$) were recruited through online advertisements at the Karolinska Institutet web page. Karyotypes of the participating individuals with TS were extracted from medical records and laboratory information systems (LIS). Inclusion criteria for participants with TS were a confirmed diagnosis of TS, age >15 years, and fluency in Swedish. The controls’ inclusion criteria were female gender, age >15, no TS

diagnosis, and fluency in Swedish. Exclusion criteria for controls were ongoing medication with known psychotropic effects, any psychiatric or neurological disorders, or suspected genetic condition.

Statistical analyses

Data visualizations indicated skewed distributions of all dependent variables (Figure 13). Choice behavior data were analyzed using linear mixed effects models (LMMs) with condition (social, non-social), block (1–5) and task order (1 or 2) as within-subjects factors and group (control, TS) as a between-subjects factor.

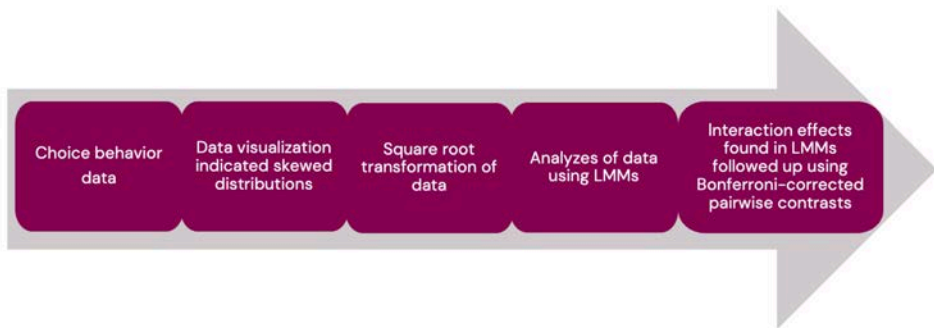


Figure 13. Statistical methods in Study III

Interaction effects between group and condition were added to test the hypothesis that social feedback would have a different effect in participants with TS, i.e., participants would respond differently to social feedback than the controls would. Additional interaction terms between group and block, and group and task order, were included to account for potential group differences, i.e., the possibility that the two groups might show different trends in their choice behavior as time in the experimental task progressed. Due to the wide age range, age was added as a covariate. To account for repeated measures (that observations within the same individual might be more similar than observations from different individuals), a random intercept for individuals was included. To adjust for degrees of freedom using LMMs, the Kenward-Roger method was used to test statistical significance, i.e., calculating p-values. In parameter α , values deviated from a normal distribution after square root transformation, and these data were therefore analyzed using non-parametric Wilcoxon tests.

Computational modelling

When studying choice behavior, computational modelling can be used to generate 'clues' as to the underlying mechanisms of the choices. By fitting mathematical formulas and computer simulations to the observable choice behavior data, the role of latent variables as underlying mechanisms influencing choice behavior can be extracted. After trying to fit plausible models to our data, the Rescorla–Wagner reinforcement learning model fit our data best, and the reinforcement learning parameters α and β were extracted in each observable choice behavior outcome.

Power analysis

A simulation-based power analysis conducted using the *simr* package in R (101) based on the observed random effects structure in Kleberg et al. (2023) indicated that the study had >80% power to detect within-group effects of conditions, given a 7% difference in the proportion of correct responses, which was considered a meaningful effect (99).

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was received by the Regional Ethics Committee of Stockholm, Sweden (drn 2018-1218/31, dnr 2020-05872)

5.5 Study IV

"Parental origin of the X chromosome in Turner syndrome: no evidence for impact on neurodevelopmental and psychiatric disorders, socio-demographic outcomes or adverse experiences during school age"

Research questions

1. How is the distribution of the parental origin of the X-chromosome in women with TS?
2. Is the phenotype of Turner syndrome affected by the parental origin of the X-chromosome? If so, how does the phenotype differ due to the maternal or paternal origin of the X-chromosome?

Study design

In this cross-sectional retrospective study, data is collected at certain time-points but includes data consisting of retrospective information see Figure 14.

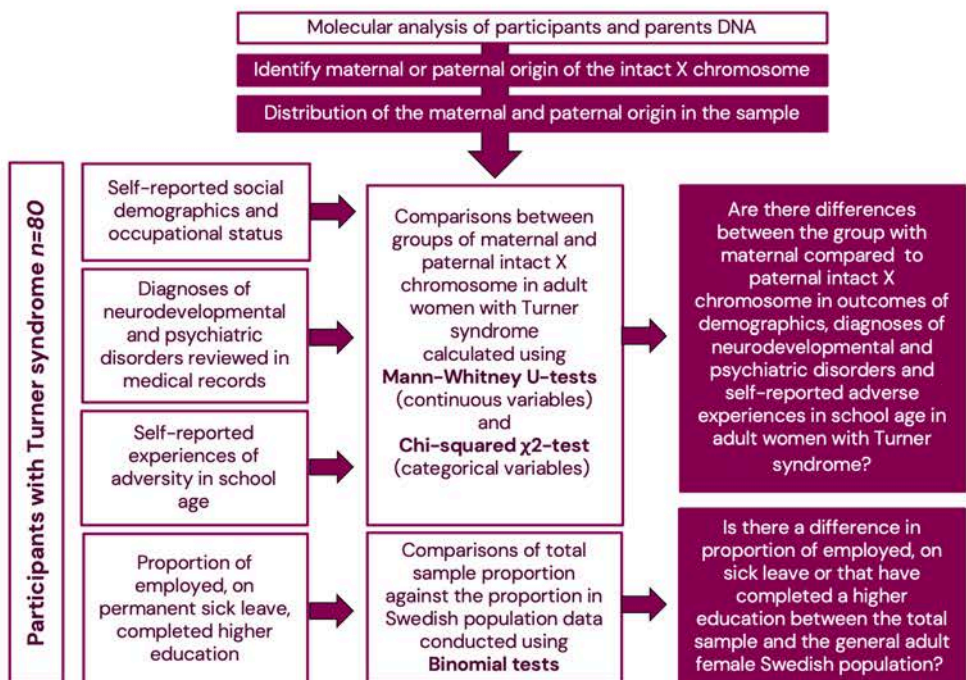


Figure 14. Study design Study IV

Outcome measures

Outcomes of sociodemographic variables were age, level of education, relationship status, and occupation. Diagnoses of neurodevelopmental and psychiatric disorders are presented in the different ICD-codes. Information of adverse experiences during school-age were answered as 'yes', 'no', or 'don't know' and presented as a categorical variable ('don't know' responses were treated as missing data). The questionnaire included questions about experiences of difficulties with spelling, writing, reading, math, and physical education at school. Further questions included whether the participant had received assistance in one or more of these academic areas or had seen a speech and language therapist, and whether the participant have had experiences of being bullied and if they did not enjoy their time in school. The origin of the retained X-chromosome in the individuals with TS were presented as maternal (Xm) or paternal (Xp) X chromosomes.

Data collection

Participants with TS were recruited at Karolinska University Hospital, at the publicly funded specialist gynecological endocrinology outpatient clinic during 2016–2023. Inclusion criteria were a diagnosis of TS regardless of karyotype, available DNA, and a living parent who was willing to participate in the study by providing a blood sample. Exclusion criteria was an inability to communicate in Swedish and a lack of parental DNA.

Self-reported questionnaires

Participants completed a brief survey on sociodemographic variables and a questionnaire about adverse school-age experiences.

Review of medical records

A review of participants' medical records and laboratory information systems (LIS) was undertaken to obtain karyotypes for each patient and diagnoses of neurodevelopmental and psychiatric disorders.

Medical records of participants were retrieved using Electronic Health Record (EHR) systems. The study was conducted at Karolinska University Hospital, where the EHR system "Take Care" is used, together with the national Swedish National Patient Summary (Nationell Patientöversikt (NPÖ)).

Molecular analysis

To determine the origin of the retained X-chromosome in the participant with TS, the individuals and one or two parents contributed with DNA extracted from peripheral blood. Chromosome preparations were made from peripheral blood lymphocytes and DNA was analyzed using quantitative fluorescence PCR (QF-PCR). Short Tandem Repeats (STR)s were used as markers for chromosomes X and Y, and with controls marked for chromosomes 13, 18, 21 using ChromoQuant SuperStAR Optima QF-PCR Kit (CyberGene AB). The PCR products were analyzed in the ABI 3500xL (Applied Biosystems) Genetic Analyzer, and the results were visualized using GeneMapper software (Applied Biosystems).

Statistics

The significance level was set to ($\alpha = 0.05$) for all analyses. P-values were not adjusted for multiple comparisons. Comparisons between groups in demographic and clinical variables were calculated using Mann-Whitney U-tests (2 groups) for continuous variables and χ^2 tests for categorical variables. In addition to group comparisons, statistical comparisons to the general adult female Swedish population were conducted for employment rate, proportion of individuals on permanent sick leave, and participants with completed higher education (102). These comparisons were conducted using binomial tests against the population proportion. In the official statistics, the rate of individuals with higher education is published in age bands covering 10-year intervals (103). We therefore calculated an adjusted population mean weighted for the age interval of our participants.

In an exploratory step, we repeated all statistical comparisons between X_m and X_p participants in the subgroup with monosomy (45,X). Results from this subgroup analysis did not differ from those found in the whole group and are therefore reported in Supplementary materials.

Power analysis

A power analysis conducted in the R package pwr indicated that the study had 80% power to detect effect sizes of Cohen's $\omega = 0.3$ in group comparisons of proportional outcomes. This can be interpreted as a medium effect size (104) and corresponds to a group difference in 30 percentage points, given the current sample size (98).

Ethics

The study was performed in accordance with the Declaration of Helsinki, and ethical approval was received by the Regional Ethics Committee of Stockholm, Sweden (dnr 2014/91-31/2, dnr 2018/431-32).

5.6 Ethical considerations

All studies included in this thesis were performed in accordance with the Declaration of Helsinki, and ethical approvals were received by the Regional Ethics Committee of Stockholm, Sweden.

Participants in **Study II, III, and IV** gave a written informed consent and were informed of their right to withdraw from the study at any time without any explanation. When using data from national registries (**Study I**) informed consent was not applicable after approval from the Regional Ethics Committee.

All personal information were kept secure and confidential, sensitive data was stored on secure servers requiring two-step authentication or kept in locked storage.

For all study participants in **Study II, III and IV**, national identity numbers and names were replaced by study identification numbers. In **Study I** Statistics Sweden holds a key to pseudonymized and de-identified data for each individual by converting the personal identification number to a study identification number where the key is not available to the researchers.

When studying rare diseases, , it's ethically important to present results in a way that protects the identity of participants and ensures that personal information is not traceable to the participants. In **Study II and IV** we grouped the karyotypes with small numbers to omit participant recognition.

6 Results

6.1 Summary of results, Study I–IV

Study I

Females with Turner syndrome are at an increased risk of neurodevelopmental or psychiatric disorders. The results showed an eightfold rise in the risk of intellectual disability and a fourfold increase in risk of autism spectrum disorder compared to controls and twice the risk of a diagnosis of schizophrenia, eating disorder, or conduct disorder.

Study II

Adult women with Turner syndrome exhibit a cognitive profile with a discrepancy between verbal and non-verbal skills, i.e. a verbal > non-verbal IQ-split. The difference between verbal and non-verbal abilities surpassed the clinical significance threshold in 77% of participants. No association between the IQ split and FSIQ or quantitative measures of ADHD or ASD symptoms was shown.

Study III

In the control group, social feedback resulted in more exploratory decisions, which in turn led to a comparatively lower rate of correct choices. However, for participants with Turner syndrome, social feedback had no impact on their decision-making behavior.

Study IV

Descriptive analyses showed that, compared to the general population, individuals with Turner syndrome appeared to have high rates of depression and anxiety, along with increased self-reported academic and social difficulties during school years. The analyses did not reveal any significant differences related to maternal or paternal origin of the X chromosome.

6.2 Table 4. Overview Participants.

Study	Sample size	Age M (SD)	Recruitment	Inclusion criteria	Exclusion criteria
Study I Participants with TS	n =1392	–	Individuals registered with an ICD of TS between 1969 and 2013 were identified from NPR	Diagnoses of TS	–
Controls	n =139 200	–	1:100 female controls matched by county and date of birth from the TPR		
Study II Participants with TS No controls	n =30	41.1 (16.7)	Women's Health Research Unit at Karolinska University Hospital	Confirmed diagnosis of TS, age >18 years and fluency in Swedish	Acquired brain injuries (dementia, stroke or brain tumors)
Study III Participants with TS	Participants with TS (final n =35) compared	33.83 (10.80)	Karolinska University Hospital and By advertising through a patient organization	Confirmed diagnosis of TS, age >15 years and fluency in Swedish	
Controls	control group of adult women without known genetic disorders (final n =37)	38.10 (15.05)	Online advertisement at the Karolinska Insitutet web page	Female gender and age >15, no diagnose of TS and fluency in Swedish	Ongoing medication with known psychotropic effects, any psychiatric or neurological disorder or suspected genetic condition
Study IV Participants with TS No control group			Karolinska University Hospital, at the publicly funded specialist gynecological endocrinology outpatient clinic during 2016–2023	Confirmed diagnosis of TS, available DNA and a living parent willing to participate in the study by providing a blood sample.	Inability to communicate in Swedish and lack of parental DNA

6.3 Study I

In **Study I**, individuals with TS (n =1392) had a higher risk of having a diagnosis of neurodevelopmental and/or psychiatric disorder in the National Patient Register (NPR) compared to matched controls (n =139 200) from the general population (OR 1.37, 95% CI 1.20–1.57) (Table 5). In comparisons to controls, a significant increased risk of having a diagnosis of intellectual disability (ID) (OR 8.59, 95% CI 6.58–11.20) or of autism spectrum disorder (ASD) (OR 4.26, 95% CI 2.94–6.18) was found, and twice the risk of a diagnosis of schizophrenia, eating disorder, or conduct disorder.

Table 5. Neurodevelopmental/psychiatric disorders in girls and women with TS compared with age-matched controls (1:100 controls). Risk presented as Odds Ratio, OR, (95% CI).

Diagnoses	Turner syndrome N(%)	Matched controls N(%)	OR (95% CI)	P
Any neurodevelopmental disorders/psychiatric disorders	283 (20.33)	21948 (15.77)	1.37 (1.20–1.57)	< .0001
Mental and behavioral disorders due to psychoactive substance use	30 (2.16)	4635 (3.33)	0.64 (0.44–0.92)	0.0091
Schizophrenia (and related disorders, including schizoaffective disorder)	29 (2.08)	1493 (1.07)	1.98 (1.36–2.88)	0.0012
Mood disorders (including bipolar, single, and recurrent depressive disorder)	79 (5.68)	8606 (6.18)	0.91 (0.72–1.15)	0.4252
Suicide attempt	19 (1.36)	2158 (1.55)	0.88 (0.56–1.39)	0.5682
Anxiety disorders (including dissociative, stress-related, and somatoform disorders)	96 (6.90)	11210 (8.05)	0.84 (0.68–1.04)	0.1034
Eating disorders	32 (2.30)	1609 (1.16)	2.03 (1.42–2.91)	0.0004
Disorders of adult personality and behavior	17 (1.22)	1720 (1.24)	0.99 (0.61–1.60)	0.9613
Mental retardation (ID)	62 (4.45)	760 (0.55)	8.59 (6.58–11.20)	< .0001
Pervasive developmental disorders (ASD)	30 (2.16)	726 (0.52)	4.26 (2.94–6.18)	< .0001
Hyperkinetic disorders (ADHD)	22 (1.58)	1732 (1.24)	1.28 (0.83–1.96)	0.2771
Behavioral and emotional disorders with onset in childhood (Conduct disorders)	26 (1.87)	1319 (0.95)	2.01 (1.35–2.99)	0.0017

When stratifying the results by the year the diagnosis of TS was registered in the NPR (see original article Study I, Table 3), individuals diagnosed with TS before 1987 or after 2002 exhibited a heightened risk of diagnosis with neurodevelopmental or psychiatric disorders compared to the controls, whereas individuals diagnosed between 1987 and 2002 did not.

Further analyses of the specific disorders revealed that there was a consistent increased risk for ASD and ID across all three stratified cohorts. However, the group diagnosed with TS before 1987 manifested the most significant risk of ASD and ID relative to controls and had a higher risk of being diagnosed with schizophrenia and/or ADHD.

Compared to the other stratified cohort groups, individuals diagnosed with TS between 1987 and 2001 were more likely to be diagnosed with eating disorders but displayed a decreased risk of diagnosed mood, anxiety, and substance use-related disorders. The cohort of individuals diagnosed with TS after 2002 was the only stratified cohort group showing an increased risk for diagnoses of conduct disorders.

6.4 Study II

In Study II, we aimed to examine the cognitive profile and compare quantitative measures of ADHD and ASD with normative data. Thirty adult women with TS completed standardized cognitive testing (WAIS-IV), self-ratings of ADHD (ASRS), and the self-screening instrument of ASD for adults (AQ).

The mean age was 41.1 years. Educational attainment within the group varied, spanning from participants who had finished elementary school to those with master's degrees. Participants' karyotype data were collected from LIS for descriptive analysis ($n = 27$). In the sample of individuals with TS, 48% had monosomy 45,X, 18.5% had mosaicism 45,X/46,XX, and 33% had structural abnormalities or other types of mosaicism categorized as 'other'.

Normative comparisons of scores of FSIQ, ASRS, and AQ

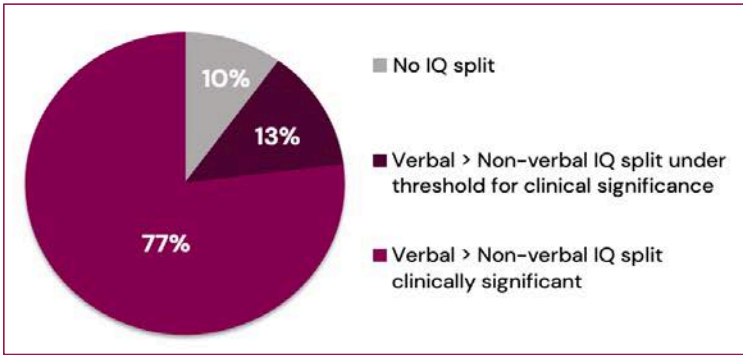
The average FSIQ score in the TS sample was 94.6 (11.4) [72–126] and compared to the average score of the general population, the TS sample had significantly lower FSIQ score ($t(29) = -2.59$, $p = .015$, $d = .47$). Additional analyses of the cognitive profile showed that lower NVIQ mean scores were displayed in the TS sample ($M = 90.37$, $SD = 13.96$, $t(29) = 3.31$, $p = .002$) but higher VIQ mean scores ($M = 107.60$, $SD = 12.57$, $t(29) = -3.78$, $p < .001$) in comparison to population norms. In the TS group, the total mean score for the full 18-item ASRS was 3.07 ($SD = 2.95$) with a range of [0–11]. When compared to the mean score of 2.1 ($SD = 3.2$) with norm data (107), there was no significant difference between the two mean scores ($t(29) = -1.80$, $p = 0.996$, $d = 0.32$). Within the TS sample, 77% had predominant scores in the ASRS inattention domain. The score on the inattention domain ($M = 12.23$, $SD = 4.86$) was significantly higher in comparison to the hyperactivity/impulsivity domain ($M = 8.8$, $SD = 4.9$), with $t(29) = 3.97$, $p = 0.012$. Scores above the screening threshold for a "likely ASD diagnosis" in the self-reported AQ were present in 1 of 30 participants (3%) in the TS sample. Mean total score for AQ was 13.2 ($SD = 6.4$) [3–31], and compared to the reported population mean of 14.88 (SD ranging from 4.2–8.0) (109), no significant difference was found ($t(29) = -1.47$, $p = > 0.99$, $d = .27$).

Table 6. Within-subject discrepancies between index scores in WAIS-IV.

Indexes	t (29)	p (Bonferroni)*	Percentage of the sample with a discrepancy above clinical cut-off
FSIQ-VCI	-9.258	<0.01	–
FSIQ-PRI	2.670	0.12	–
FSIQ-WMI	2.667	0.12	–
FSIQ-PSI	2.371	0.25	–
VCI-PRI	6.905	<0.01	57%
VCI-WMI	7.417	<0.01	47%
VCI-PSI	6.922	<0.01	43%
PRI-WMI	-.052	>0.99	27%
PRI-PSI	-.119	>0.99	17%
PSI-WMI	-.085	>0.99	17%

Strengths and weaknesses in the cognitive profile—WAIS-IV indices

Comparisons between the WAIS-IV indexes and between specific indexes and FSIQ are shown in Table 6. The TS sample presented higher scores in the VCI compared to PRI, VMI, and PSI. According to the WAIS-IV manual, a clinically significant difference between various index scales is seen in 15% or fewer in the normative population (106). However, in the TS sample, 77% exhibited a clinically significant discrepancy between verbal IQ (VCI) and one or more of the other indices (PRI, WMI, and PSI) (Figure 15). Higher VCI scores compared to PRI scores were displayed in 90% of participants (27 out of 30) and in this group, 57% exceeded the threshold for clinical significance.



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Figure 15. Percentage of the sample with a verbal > non-verbal IQ split.

Strengths and weaknesses in the cognitive profile—WAIS-IV subtests

Intra-individual comparisons of subtest scores and the mean score for all 10 subtests (see Table 7), reveals that all three VCI subtest scores were significantly higher compared to remaining subtests. In contrast, PRI subtest “block design” and PSI subtest “symbol search” showed significantly lower scores than participants’ individual mean score of all 10 subtests.

Table 7. Intra-individual comparisons of subtest score with the mean score for all 10 subtests.

Index score	Subscale	Subscale score M (SD)	t (29)	p (Bonferroni)*
Verbal Comprehension (VCI)	Similarities	12.75 (2.78)	-11.26	<0.01
	Vocabulary	10.57 (2.16)	-4.62	<0.01
	Information	10.50 (2.43)	-3.55	0.01
Perceptual Reasoning (PRI)	Block Design	7.97 (2.36)	4.15	<0.01
	Matrix Reasoning	9.2 (3.514)	0.16	>0.99
	Visual Puzzles	8.13 (2.50)	2.95	0.06
Working Memory (WMI)	Digit Span	8.50 (2.26)	2.64	0.13
	Arithmetic	8.57 (2.65)	1.91	0.67
Processing Speed (PSI)	Symbol Search	7.90 (2.23)	4.16	<0.01
	Coding	8.43 (2.19)	2.58	0.15

Note: p-values refer to paired sample t-tests comparing each subscale to the mean of all 10 subscales for each individual. If paired samples t-tests revealed a significant difference, the subtest was deemed either a strength or weaknesses.

*p-value is corrected with Bonferroni analysis in groups of 10. Bold values indicate statistical significance at the p <0.05 level.

Cognitive profiles associated with FSIQ average or symptoms of ADHD and ASD

There were no significant correlations between the verbal > non-verbal IQ split and total score of FSIQ ($r(28) = -.087, p = .648$), ASRS score ($r(28) = .132, p = >0.99$) or AQ score ($r(28) = .247, p = >0.99$). Bayes factors showed moderate support for the null hypothesis of the relationship between the IQ split and ASRS scores, and between IQ split and AQ scores.

Moreover, no significant association was found between VCI and the total scores of ASRS ($r(28) = .323, p = .82$) or AQ ($r(28) = .148, p = >0.99$). Similarly, PRI did not correlate significantly with total scores of ASRS ($r(28) = .181, p = >0.99$) or of AQ scores ($r(28) = -.088, p = >0.99$). Additionally, there was no correlation between ASRS and AQ scores ($r(28) = 0.297, p = >0.99$).

6.5 Study III

In Study III, results of feedback on choice behavior and learning were compared between participants with TS ($n = 35$) and a control group ($n = 37$) using an experimental reinforcement learning task. The participants' ratings of their affective experiences of receiving feedback were initially added as a covariate but did not have an effect on the results.

Reaction times

Analyses of reaction times showed that participants across groups responded quicker during later trials compared to early trials and were quicker in the non-social compared to the social condition. Similarly, reaction time variability decreased over the course of the experiment, and was smaller in the non-social than in the social condition. No main- or interaction effects involving groups were found, indicating that these effects did not differ between women with TS and controls.

Choice behavior outcomes

While percent correct reflects task performance, percent volatility, percent switch-win and percent switch-lose provide measurements of strategy and cognitive processes involved in solving a task. A computational modelling analysis was conducted to examine potential underlying mechanisms of observed choice behavior. Following model comparisons as recommended by Wilson & Collins (2019), data were modelled using the Rescorla-Wagner model (105). This model has two parameters: 1) learning rate (α) which governs the degree to which the participant is influenced by the most recent feedback, and 2) exploration, (β) which governs the degree of exploratory choice behavior or deviance from the learned expectations about rewards.

Lower β indicates a higher degree of exploration. For effective learning in a probabilistic environment, the individual needs to balance between sticking to their established strategy (exploitation) and occasionally diverging from it to further explore the environment (exploration), referred to as the exploration-exploitation balance.

%Correct—Percent of trials where the choice was more likely to receive a winning point

A significant main effect of block was found, with a higher percentage correct during later trials [$b = 2.07$, $se = 0.65$, $t = 2.71$, $p = .007$] but no significant main effects were found for condition, group, or order. In summary, the percentage of correct choices increased in both groups during later trials. No significant interactions between group and block, group and order, or condition and block, but a significant group and condition interaction was found [$b = 5.17$, $se = 2.23$, $t = 2.23$, $p = .026$]. As shown in Figure 16, pairwise follow-up tests showed that the control group had a higher percent correct in the non-social condition compared to the social condition [$b = 5.01$, $se = 1.50$, $t = 3.45$, $p = .001$] but no effect of condition was found in the TS sample [$b = -0.16$, $se = 1.64$, $t = 0.13$, $p = .898$]. In summary, the control group had a higher percent correct in the non-social compared to the social condition, whereas no effect pertaining to condition was found in the TS group.

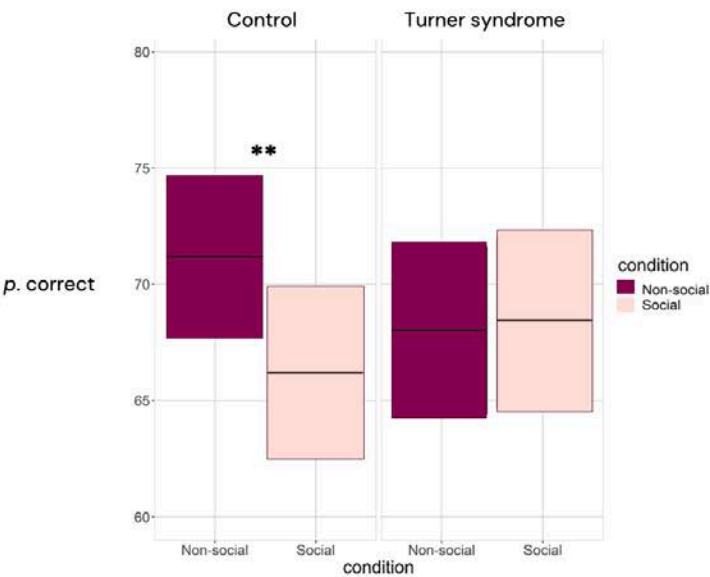


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Figure 16. "Pairwise follow-up tests: percent correct choices by group and condition. Note: Crossbars show estimated marginal means and 95% confidence intervals. Note ** $p < .05$ Bonferroni corrected."

%Volatility—the proportion where the participants switched from the previously choice

No significant main effects were found for condition, group, or order. The main effect of the block was significant, indicating lower percent volatility during later trials [$b = 2.51$, $se = 0.69$, $t = 3.34$, $p = .001$]. No significant interaction effects were found.

%Switch-win—the proportion of switches following wins

No significant effects were found in main effects or interaction effects.

%Switch-lose—the proportion of switches following losses

As the experiment went on, all participants were less likely to switch between the choices after losses [main effect of block: $b = -5.12$, $se = 0.97$, $t = -5.35$, $p < .001$]. No significant main effects were found for condition, group, or order. Significant interaction effects were found between group and condition [$b = -7.57$, $se = 3.34$, $t = -2.44$, $p = .015$] and block and condition [$b = 3.15$, $se = 1.15$, $t = -2.55$, $p = .011$], but not for group and order or group and block.

Learning parameter α

For the parameter α , neither the TS sample or the control group showed significant differences in learning rates between social and non-social conditions.

Exploration rate parameter β

No significant main effect of group or order were found but a significant main effect of condition [$b = 0.54$, $se = 0.2$, $t = 2.89$, $p = .005$] where a difference in the balance between exploration and exploitation was found between social and non-social conditions. The group-by-order interaction was not significant, but a significant interaction between group and condition was found [$b = 0.61$, $se = 0.29$, $t = 2.16$, $p = .035$]. Bonferroni-corrected follow up comparisons showed higher β (more deterministic choices, less explorative choices) in the control group in the non-social condition than in the social condition [$b = 0.56$, $se = 0.20$, $t = 2.89$, $p = .01$], whereas no effect of condition was found in the TS group [$b = -0.07$, $se = 0.21$, $t = 0.27$, $p > .80$], see Figure 17.

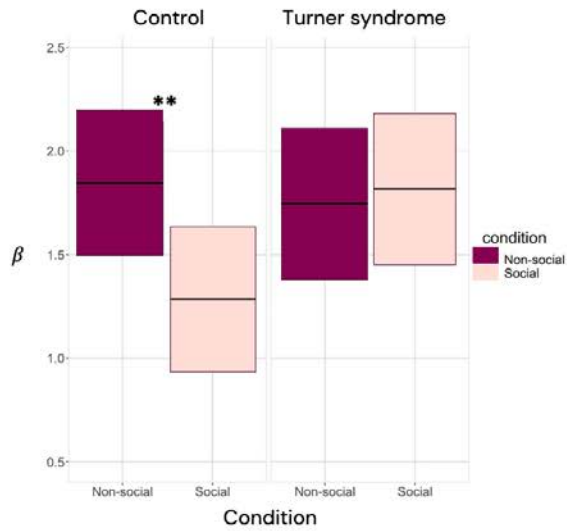


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Figure 17. "Bonferroni-corrected follow up comparisons. β in the control group and TS group as a function of condition. Note: Crossbars show estimated marginal means and 95% confidence intervals. Note ** $p < .05$ Bonferroni corrected."

6.6 Study IV

In Study IV, the parental origin of the X chromosome was identified in 80 participants with available DNA. The parental origin of the X chromosome was of maternal origin (Xm) in 70.3% of participants and of paternal origin (Xp) in 29.7%. No significant differences were found in the distribution between Xm and Xp in relation to participants' karyotypes as can be seen in Table 8.

Table 8. Distribution of karyotypes in the whole sample and in participants with Xm and Xp.

Karyotype	Descriptive Statistics			Group Comparison (Xm ≠ Xp)	
	Total sample	Xm	Xp	χ^2 test (df =1)	p
Karyotype known (n/max)	74/80	52/57	22/23	$\chi^2 = 0.462$	0.417
Distribution of known karyotypes (max =74) *					
45,X	39/74 (52.7%)	29/52 (55.8%)	10/22 (45.5%)	$\chi^2 = 0.66$	0.417
45,X/46,XX	2/74 (2.7%)	1/52 (1.9%)	1/22 (4.6%)	$\chi^2 = 4.04$	0.525
45,X/46,XY	5/74 (6.8%)	5/52 (9.6%)	0/22 (0%)	$\chi^2 = 2.27$	0.132
Short arm (Xp) deletions	4/74 (5.4%)	2/52 (3.9%)	2/22 (9.1%)	$\chi^2 = 0.832$	0.362
Long arm (Xq) deletions	5/74 (6.8%)	3/52 (5.8%)	2/22 (9.1%)	$\chi^2 = 0.27$	0.603
Isochromosomes	13/74 (17.6%)	9/52 (17.3%)	4/22 (18.2%)	$\chi^2 = 0.01$	0.928
Ring Chromosomes	3/74 (4.1%)	1/52 (1.9%)	2/22 (9.1%)	$\chi^2 = 2.04$	0.153
Other	3/74 (4.1%)	2/52 (3.9%)	1/22 (4.6%)	$\chi^2 = 0.02$	0.889

Sociodemographics

Self-reported demographics are presented in Table 9. No significant differences were found in the TS sample between individuals with Xm and Xp in relation to any of the demographic variables. The employment rate among the participants was similar to the employment rate of women in Sweden in 2019, which was 79% (binomial test: $p = 0.676$). Likewise, the proportion of participants on permanent sick leave was close to that of the general female population, at around 10% (binomial test: $p > 0.90$). The proportion of participants with TS had a similar proportion of participants with higher education compared to the general Swedish female population (50.10%, binomial test: $p = 0.605$), after adjusting for age differences, 50.10% (binomial test: $p = 0.605$).

Table 9. Descriptive statistics of age and self-reported sociodemographics, comparisons.

Demographics		Descriptive Statistics Xm/Xp		Group Comparison	
	Total sample n =80*	Xm n =57	Xp n =23	Test statistic	p
Age Mean (SD) [Range]				Mann- Whitney Test (W, df =72)	
Age at the end of the medical records review	38.2 (9.6) [21–64]	40.1 (10) [24–64]	33.7 (7.0) [21–46]	W =882	0.016
Age when completed testing and questionnaires	32.70 (9.7) [18–57]	34.4 (10.2) [18–57]	28.4 (6.6) [19–41]	W =866.5	0.025
Social demographics Frequency (%)				χ^2 test (χ^2 ,df =1)	p
Married/partner	42/79 (53.2%)	33/56 (58.9%)	9/23 (39.1%)	2.566	0.109
Occupation at the time of assessment					
Employed	60/78 (76.9%)	44/55 (80.0%)	16/23 (69.6%)	0.995	0.319
University student	12/79 (15.2%)	6/56 (10.7%)	6/23 (26.1%)	2.991	0.084
High-school student	3/79 (3.8%)	1/56 (1.8%)	2/23 (8.7%)	2.131	0.144
Permanent sick leave >50%	8/80 (10%)	6/57 (10.5%)	2/23 (8.7%)	0.061	0.805
Completed university degree	42/78 (53.9%)	32/56 (57.1%)	10/22 (45.5%)	0.868	0.351

Medical records review

History of diagnosed neurodevelopmental and psychiatric disorders was reviewed by collecting information from medical records and is presented in Table 10. No significant differences were found in the TS sample between individuals with Xm and Xp in demographics, as can be seen in see Table 9.

Table 10. Diagnosis of neurodevelopmental and psychiatric disorders in the study group, presented together with group comparison between parental origin of X chromosome.

Diagnosis obtained in medical record review	Descriptive statistics Frequency/Valid n (percent, %)			Group comparison	
	Total sample n =80	Xm n =57	Xp n =23	Test statistic χ^2 df =1	p
Neurodevelopmental disorders					
Attention Deficit Hyperactivity Disorder	9/80 (11.3%)	6/57 (10.5%)	3/23 (13.0%)	0.104	0.747
Autism Spectrum Disorders	8/80 (10%)	4/57 (7.1%)	4/23 (17.4%)	1.959	0.162
Mild Intellectual disability	1/80 (1.3%)	1/57 (1.8%)	0	0.416	0.519
Psychiatric disorders					
Depression	27/80 (33.8%)	17/57 (29.8%)	10/23 (43.5%)	1.366	0.242
Anxiety	29/80 (36.3%)	20/57 (35.1%)	8/23 (39.1%)	0.016	0.734
Depression and/or Anxiety	32/80 (40%)	21/57 (36.8%)	11/23 (43.5%)	0.824	0.364
Stress related disorders	18/80 (22.5%)	13/57 (22.1%)	5/23 (21.7%)	0.011	0.918
OCD	3/80 (3.8%)	2/57 (3.5%)	1/23 (4.4%)	0.032	0.858
Schizophrenia	2/80 (2.5%)	2/57 (3.5%)	0/23	0.828	0.363
Bipolar disorder	1/80 (1.3%)	1/57 (1.8%)	0/23	0.409	0.523
Sleep disorder	9/80 (11.3%)	6/57 (10.5%)	3/23 (13.0%)	0.104	0.747
Eating Disorders	5/80 (6.3%)	4/57 (7.0%)	1/23 (4.4%)	0.199	0.655

Experiences of academic and social adversity in school age

The self-reported experiences from school age are presented in Table 11. No significant differences in the reported experiences were found in comparisons between individuals with Xm and Xp.

Table 11. Self-reported experiences of adversity in school age with comparisons between groups of parental origin.

Self-reported experiences of adversity in school age	Frequency (percent, %)	Descriptive Statistics Xm/Xp		Group Comparison	
		Xmn=53±.	Xp n =21±	χ^2 test (df =1)	p
Spelling difficulties	16/73 (21.9%)	9/53 (17.0%)	7/20 (35%)	2.755	0.097
Writing difficulties	3/74 (4.1%)	1/53 (1.8%)	2/21 (9.5%)	2.255	0.133
Reading difficulties	5/74 (6.8%)	4/53 (7.6%)	1/21 (4.8%)	0.185	0.667
Mathematical difficulties	29/73 (39.7%)	18/52 (34.6%)	11/21 (52.4%)	1.972	0.160
Speech difficulties	5/73 (6.3%)	5/53 (9.4%)	0/20	2.026	0.155
Physical education difficulties	26/72 (36.1%)	17/51 (33.3%)	9/21 (42.9%)	0.585	0.444
Seeing a speech/language therapist	18/73 (24.7%)	16/52 (30.8%)	2/21 (9.5%)	3.634	0.057
Special education/support	31/72 (43.1%)	19/51 (37.3%)	12/21 (57.1%)	2.400	0.121
Experience of being bullied	31/68 (45.6%)	23/48 (47.9%)	8/20 (40%)	0.357	0.550
Not enjoying school	21/72 (29.2%)	15/52 (28.8%)	6/20 (30.0%)	0.009	0.923

7 Discussion

The main findings and interpretation are presented according to genotype and the different themes that constitute the phenotype in this thesis as presented in Figure 18.

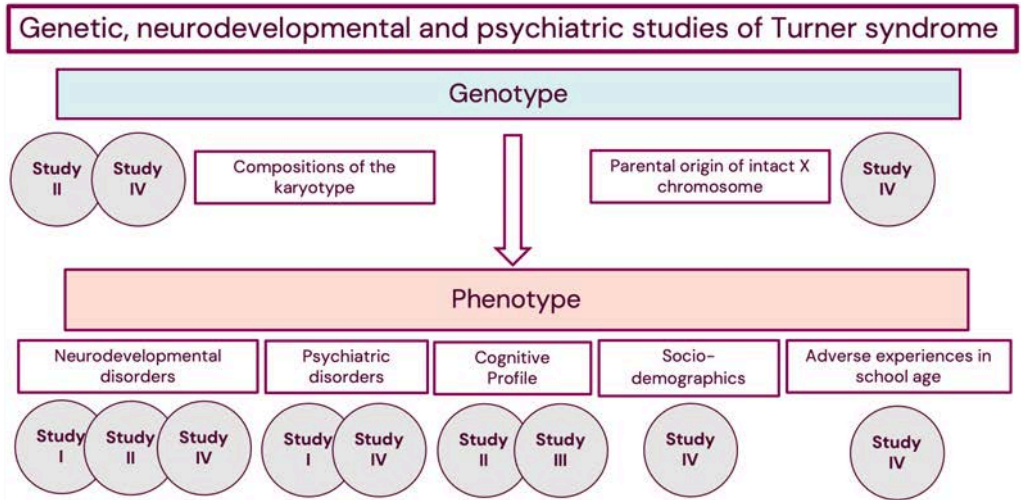


Figure 18. Overview of the relationships between genotype, phenotype, and related themes examined in this thesis.

Composition of the karyotype

Previous studies have found that specific karyotypes are associated with risk of neurodevelopmental disorder (77, 78), however, due to study design (**Study I**) and small sample sizes (**Study II, III and IV**) no conclusions can be drawn on the impact of karyotype on the present findings.

Parental origin of the retained X chromosome

In **Study IV**, we examined a possible impact of the parental origin of the X chromosome in relation to phenotype presented in this thesis (Figure 18). However, our analysis did not reveal any notable differences across the various phenotypic themes explored that could be attributed to the origin of the remaining X chromosome.

This result is aligned with previous studies reporting no significant impact of parental origin of the X chromosome in neurodevelopmental disorders (37, 86) on outcomes such as education level, occupational status, or having a partner (80). In contrast, several previous studies have shown evidence of phenotypic

differences between Xm and Xp related to the phenotypes explored in this thesis. However, most studies have been focused primarily on participants with monosomy 45,X karyotypes (61, 81-83). In this study we examined phenotypes and distribution of Xm and Xp across various karyotypes and performed a sub-analyses in the group monosomy X (45,X). Despite this, no significant differences were found in outcomes that could be attributed to Xm or Xp, nor did the distribution of Xm and Xp differ between karyotypes.

Neurodevelopmental disorders

Study I showed an increased risk of receiving a diagnosis of ASD and ID, but no significant risk of ADHD compared to the controls. In **Study II**, even if symptoms on screening measures reached thresholds for ADHD and ASD in a higher proportion than what would be expected in the general population, the absolute number of positive cases was low. Similarly, in **Study IV**, our medical review based on medical records showed relatively high registered frequencies of ADHD, ASD, and ID. While these results support the notion that women with TS may be at elevated risk for neurodevelopmental disorders, these numbers should not be taken as an estimation of prevalence in the general TS population due to the small sample sizes.

The prevalence of ADHD in individuals with TS is relatively well studied, at least in children and adolescents, with a majority of studies reporting findings of a higher prevalence of ADHD in TS compared to the general population (36-38). Surprisingly, no such increased risk of ADHD was found in our population-based cohort study (**Study I**). ADHD might be underreported in the Swedish National Patient Register, but it is also possible that previous reports based on smaller clinical samples have overestimated the risk of ADHD due to recruitment biases.

Previous studies of ADHD symptoms in TS have showed hyperactivity and impulsivity to be more prominent than inattention in children and teenagers with TS (36, 37), but studies in adult women with TS are lacking. When comparing ASRS scores between domains of inattention and hyperactivity/impulsivity in **Study II**, results showed that 77% of participants had dominating challenges in inattention compared to in hyperactivity/ impulsivity. However, without longitudinal studies of ADHD of individuals with TS, it remains uncertain whether, as proposed for the general population, ADHD symptoms typically transition from being predominantly hyperactive during childhood to becoming less pronounced in adulthood (106, 107).

In **Study I**, 2.16 % of the TS cohort had a diagnosis of ASD, which is in line with several studies over the past few decades indicating a heightened risk of ASD in individuals with TS (45, 46, 56, 108). In a recent study, Wolstencroft et al. (2022) reported that 23% of children and adolescents with TS met diagnostic criteria for ASD in the diagnostic interview DAWBA (Development and Wellbeing Assessment) (46). However, in adult women with TS, de Vries et al. (2019) and Leidmeier (2020) showed results similar to our findings in **Study II**; namely that the AQ scores of adult women with TS surpassed the clinical threshold for ASD in 6.6% of the women with TS, indicating higher scores than the norm population (47, 48). Additionally, Kremen et al. (2023) reported an elevated prevalence of ASD diagnoses (4%) in a review of medical records when compared to the norm population (50). An even more elevated likelihood of a diagnosis of ASD (10%) was observed in our review of medical records in **Study IV**, albeit with a significantly smaller sample size.

While existing literature in individuals with TS indicates that individuals with TS typically have a FSIQ within the normal range (53, 54, 109, 110), **Study I** showed a higher risk of ID, with 4.45% of the TS cohort diagnosed with ID. In contrast, participants in **Study II** had an average FSIQ score that, while slightly below the average for the general population, was still within the normal range, and none of the participants scored below an FSIQ of 70, which is typically considered a threshold for ID (35). Nevertheless, earlier research suggests an elevated risk of ID, particularly associated with karyotypes that have a ring chromosome (77, 78). Since the karyotypes of the individuals in **Study I** were undisclosed, we cannot make any definitive conclusions based on these findings in relation to karyotype.

Furthermore, in **Study I**, when stratifying the cohort by the year of initial TS diagnosis (ranging between 1969 and 2013), only the risks of ID and ASD were consistently higher in all cohorts. Notably, the cohort comprising individuals diagnosed before 1987 exhibited the highest odds ratios for both ASD (8.56 (3.92–18.71), and ID (12.0 (6.78–21.07)), in comparison to the subsequent cohorts from 1987–2001 and >2001. This cohort (<1987) was the only cohort showing a significant risk of schizophrenia. Considering the earlier years within this timespan, the coverage of the registers was incomplete and included only inpatient care, prompting the hypothesis that genetic testing was more frequently conducted in individuals presenting with a more severe phenotype at inpatient treatment facilities. This might illustrate a historical perspective of the knowledge of TS and the diagnostic tools available at the time, rather than a true increase in the

prevalence of ID, ASD or schizophrenia in TS. However, it is worth noting that in a recent study from Denmark, Sánchez et al. (2023) found similar results to our **Study I** when they integrated genotype data with population-based registries (38). Sanchez et al. (2023) enabled the inclusion of individuals who, despite not being clinically diagnosed with TS, displayed a detectable TS genotype. The risk of psychiatric disorders was interestingly consistent and as elevated for the 7% undiagnosed individuals as it was for the rest of the Danish TS sample (38).

Psychiatric disorders

Study I reported a doubled risk of schizophrenia compared to the general population, at 2.08%, which aligns closely with the findings from **Study IV**, where 2.5% of participants were diagnosed with schizophrenia. This is notable, given the scarcity of research on the prevalence of schizophrenia and related disorders within the TS population. Yet, a preceding study did document a 1% incidence rate of schizophrenia in a cohort of 325 individuals with TS (47).

Furthermore, **Study IV**, showed that a high proportion of the 80 studied women with TS had been diagnosed with depressive disorders (33.8%), anxiety disorders (36.3%), and stress-related disorders (22.5%) in a review of medical records. In contrast, **Study I** displayed no significantly higher risk of being diagnosed with mood disorders (bipolar- and depressive disorders) or anxiety disorders in the TS cohort compared with controls. Previous studies of anxiety and depression in individuals with TS have, in contrast to **Study I**, shown elevated risks for both disorders, which align with the findings from **Study IV** (33, 48–51). In a review, Morris et al. (2020) present a prevalence of depressive disorders ranging from 36% to 65.2% in adults with TS syndrome, exceeding the 33.8% reported in **Study IV** (33). In addition, in a retrospective review of medical records, Kramer et al. (2023) found a prevalence of 17.4% of diagnosed anxiety disorders in a group of TS that also included younger individuals than were included in **Study IV** (50).

Elaborating on the discrepancies between the outcomes of depression and anxiety disorders in **Study I** and **Study IV**, the review of medical records in **Study IV** also encompassed medical records from primary care. The incorporation of primary care data shed light on the prevalence of conditions such as anxiety, depression, and stress among women with TS; diagnoses that may have been missing in registry-based studies due to coverage. Nevertheless, the lack of a control group in **Study IV** prevents it from addressing whether women with TS have a higher likelihood of psychiatric conditions compared to the general

population. However, regarding depression, most studies indicate a lifetime prevalence of 15%–20% in the general female population (111, 112) which is lower than the proportion found in **Study IV**. Nonetheless, more recent studies indicate a considerably higher lifetime prevalence of around 34% (113, 114) which aligns more closely with the findings in **Study IV**.

Of note, prevalence rates were considerably higher for depression and anxiety in **Study IV** than those found in **Study I**, indicating that a high proportion of women with TS receive treatment for depression and anxiety in healthcare services not covered by the national registers used for epidemiological studies.

Cognitive profile

When examining the participants VIQ > NVIQ split further in **Study II**, notably, 77% of participants with TS displayed a split exceeding cut-off for clinical significance, meaning that the difference in scores between domains is statistically large enough that there is a measurable effect on the individual's functioning (91). Nevertheless, the impact of the uneven cognitive profile in actual adaptive functioning in TS is unclear.

The cognitive phenotype of TS has in the broad literature been characterized by relatively stronger verbal than nonverbal abilities and challenges related to executive functions and attention (52, 53). In the comprehension of the TS phenotype, it is crucial to understand how the cognitive profile is related to other phenotypic characteristics, especially in life domains where cognitive skills are essential. **Study II** contributes to this research question by examining the association between VIQ–NVIQ-split and symptoms of ADHD and ASD. No significant correlations were found, suggesting that these two domains may be Independent In TS.

When investigating objective outcome measures of social compared to non-social feedback in the reinforcement task in **Study III**, individuals with TS were less receptive to social feedback, thereby indicating a lower receptiveness to social cues compared to the broader population. Alterations in reinforcement learning have also been observed in ASD (115), which raises the possibility that changes seen in reinforcement learning may be a common factor contributing to social challenges in both individuals with ASD and TS. Social feedback influence many aspects of social behavior, and perceiving and responding to social feedback based on the input of others is important throughout the lifespan (116).

Impairments in the understanding of social cues leading to difficulties in establishing relationships may result in social isolation, and therefore constitute a risk factor for depression (11, 117).

The reduced influence of social feedback on reinforcement learning in TS, as seen in **Study III**, could potentially be affected by difficulties in executive function, especially the executive control of attention that affects focus on certain parts of a stimulus (118). This hypothesis suggesting deficits in integrative executive functions is consistent with findings from **Study II**, where tasks requiring simultaneous functioning of cognitive domains were identified as areas of weakness. In addition, deficits in executive abilities are also supported in **Study II** by the self-reported challenges in attention-related areas in ASRS. The findings indicate that in the control group, social feedback prompted more exploratory choices, leading to diminished learning compared to non-social feedback. However, in TS, social feedback didn't impact learning. To further elaborate on the understanding of the phenotype in TS we applied computational modeling in **Study III** to reveal mechanisms undergirding choice behavior. New innovative methods with objective descriptions and insights into underlying mechanisms could reveal new knowledge in the field. There is a rising trend in employing computational modeling in diverse fields to study cognitive functions. Computational psychiatry is an emerging field of computational techniques in multiple types of data, such as genetics, cognitive measures, and neuroimaging, in order to further understand the relationship between neurobiology, the environment, and symptoms of psychiatric disorders (119).

Adverse experiences in school and sociodemographics

Study IV showed that almost 45% of women reported having been bullied during their school age years. While direct statistical comparisons with the general Swedish population are hindered by the absence of comparable outcome measures, Schäfer et al. (2004) reported a 28% prevalence of individuals in a European sample being bullied in school (120), and a similar proportion, 27.9%, was found by Green et al. (2018) in the USA (121). In earlier literature it has been discussed and debated whether social withdrawal could be secondary to stigma associated with appearance characteristics, short stature, or infertility (117, 122, 123). However, exposure to bullying can also be seen in a broader perspective of social challenges where various aspects of social interaction and friendship are challenged. In recent studies by Wolstencroft et al. (2020), young women with TS

reported difficulties in social communication when interviewed (56) and further in Wolstencroft (2022) parents to participating individuals with TS reported challenges in their child's abilities to both make friends and keep them (46).

Moreover, the participants in **Study IV** reported challenges in school, and 43.1% of participants reported a need for support or special education at some point. Notably, despite the many challenges reported during their school years, particularly in subjects such as mathematics (39.7%), a majority of participants completed higher education (53.9%).

Despite adverse experiences in school and educational challenges, the participants in **Study IV** demonstrated high educational achievements and employment rates, an occupational and educational pattern also shown by Stochholm et al. (2012) in Denmark (124), Gould et al. (2013) in the USA (80), and Noordman (2021) in a European multicenter study (125). However, we lacked the controls or population-based metrics to directly compare marital status, whereas the three larger studies mentioned above showed findings of fewer women with TS living together with a partner or married compared to the general population (80, 124, 125). When comparing long-term sick leave in TS against the Swedish female population, the proportions were found to be consistent, an outcome measure that could not, however, be compared to that of other countries.

8 Methodological considerations

Designing studies, analyzing data, and interpreting results in rare conditions, such as TS, may require special methodological considerations to ensure the validity, reliability and interpretability of results due to small sample sizes. Findings in a study can only be generalized if the sample studied is representative of the larger population (i.e. no selection bias), and the conditions of the study do not unduly influence the results (i.e. high external validity).

One limitation with studies conducted in small populations concerns whether there is sufficient statistical power to detect differences or associations in groups. It could be argued that failure to reach significance in an analysis can be due to insufficient power rather than the absence of association, (i.e. type II error), or that many sub-analyses are conducted in a study so that the possibility increases for some significant findings simply due to random variation, (i.e. type I error). Overall, integrity is required from the researcher to approach the results with caution.

Sample size and power

The unselected inclusion of individuals with TS in Sweden in the nationwide population-based cohort design used in **Study I** is a strength. To our knowledge **Study I** was, at the time published, the largest study to examine diagnoses of neurodevelopmental and psychiatric disorders in TS. Nevertheless, due to TS being a rare disorder and with varying register coverage, the small sample sizes especially when the cohort was stratified is a limitation.

In **Study II** and **IV**, the sample size did not allow statistical comparisons between subgroups based on karyotypes. However, comparisons of outcomes within the groups and with population norms were applied in **Study II** and **IV**. However, as mentioned before, due to the small sample size, these numbers should not be considered as accurate estimates of prevalence in the general population. In **Study III** a control group was recruited, and statistical group differences were observed, but the within-group variability was large and the results must be interpreted with caution.

Selection bias

In all **Study I–IV**, there is a risk of ascertainment bias and Berkson's bias (126). Individuals with TS are more likely under regular care and more frequent visit

hospital setting than women in the general population, thus more surveillance for neurodevelopmental and psychiatric symptoms and disorders.

However, **Study I**, being a population-based register study, does not have a risk as **Study II, III and IV** of being biased by the "Healthy Volunteer Effect". This selection bias arises because individuals with more severe health issues or additional symptoms are typically less inclined to participate in research, particularly if the studies require interventions or a considerable dedication of time.

In the cross-sectional retrospective **Study IV** where the participants self-reported previous experiences from school age there is a risk of recall bias, a systematic error that occurs when the participants do not remember previous experiences correctly or omit details.

Information bias

Information bias emerges due to inaccuracies in data measurement or collection, risking incorrect conclusions when utilized in the analysis. In **Study I** the exclusion of primary care data from the NPR might lead to potential underestimation of certain disorders. In **Study II** the screening measure AQ, has a low specificity and thus a risk of a high rate of false positives in outcome. In addition, in **Study II** we utilized data from English-speaking countries for comparisons due to absence of Swedish normative data for ASRS and AQ. In **Study III** a limitation was that we were not able to observe the participants or the environment when they completed the task and no qualitative information about the participants' experiences when performing the task was collected. In **Study IV**, the self-reported questionnaire had not been validated or tested with a control group, and thus its psychometric properties are unassessed.

In **Study IV** the diagnoses were collected from medical records, a strength that supports the validity of the diagnoses. Nevertheless, the incompleteness of the medical records is a limitation, and the numbers of neurodevelopmental and psychiatric diagnoses collected in **Study IV** are probably underestimated. Medical records from gynecological specialist care were available in all participants but primary care records were available in 76/80 participants and to varying extents.

9 Clinical implications and future perspectives

Study I adds new knowledge by indicating higher prevalence of ID and ASD than previously reported in a population-based cohort and **Study IV** revealed a high proportion of women with TS had been diagnosed with psychiatric and neurodevelopmental conditions. This informs clinicians of the importance of investigating symptoms of psychiatric and neuropsychiatric disorders in women with TS as a diagnosis may open up some sources of support and allow the patient a better understanding her behavior.

However, **Study I** and **IV** provide an inconsistent view of the actual prevalence of neurodevelopmental and psychiatric disorders with several conflicting results and this is likely due to the degree of coverage of registries and medical record systems that are not unified, and the information is therefore limited to the individual medical unit. Diagnoses distributed in the primary care or private facilities might not be captured in the registers, at least not in Sweden. Thus, the prevalence of diagnoses made in outpatient settings as general practitioners or privately practicing psychiatrists may be completely omitted. This aligns with the findings in **Study IV** where data of diagnoses from outpatient services, at least to some extents, also were included by reviewing medical records. Instead of observing a lower or not significant prevalence compared to the control in **Study I**, there was a noticeable increase in individuals with diagnoses of anxiety, depression, and stress-related disorders in **Study IV**. This emphasizes to clinicians and researchers that the various sources of information often fail to provide a uniform description of the individual. It also underscores the need for research to encompass various methodologies and to exercise caution when drawing conclusions from a single method.

In **Study II** the cognitive examination of adult women in TS showed a clinically significant uneven cognitive profile. Reliable and objective ways to measure social skills and challenges are essential. However, comparisons between different studies or monitoring progress over time are complicated due to diverse definitions of social skills and the different methods used to assess it. Most tools used to measure social abilities rely on the individuals self-reporting and there's a notable difference in the self-evaluated social experiences of girls and teenagers with TS compared to observations made by parents or teachers. The self-reports of girls and adolescents often indicate fewer social challenges and an over-estimation of their own social skills, a tendency well-documented in children and adolescents with TS (46, 56). To evaluate whether this discrepancy in self-perception persists into adulthood in women with TS is more challenging, as obtaining information provided by guardians or other observers is less likely.

Future studies should ideally combine measures of everyday functioning, self-report, and cognitive assessments including experimental research. This could give novel insights into the factors associated with cognitive alterations in TS.

Online data collection as used in **Study III** offers a practical method for gathering data and allows for the inclusion of participants who are not in close connection to research centers or who suffer from social difficulties and therefore avoid in-person settings. This approach is notably valuable in studies involving rare genetic conditions, where it is often a challenge to recruit a larger number of participants. An intriguing area for future research could be examining social and non-social feedback for both wins and losses. Specifically, for individuals with TS, who is suggested to have challenges in precept faces expressing anger or fear, the impact of receiving social feedback—such as a facial expression displaying a negative emotion after a loss would be worth exploring further.

In **Study IV**, a large proportion of women with TS reported negative experiences from school age such as needing support or special education and being victims of bullying. An important issue for future studies is to identify risk factors for these negative experiences during school age, which highlights the need for multidisciplinary support in school for girls with TS.

In summary, the overall findings of this thesis indicate that assessment of intellectual and cognitive functions from an early age is of great importance. Increased psychiatric vigilance within the health care system must be part of lifelong health care for women with TS, particularly in adulthood. In the school environment, resources are needed to be able to offer correct treatment, training interventions and adaptations in everyday life. Further investigation of the relationship between genotype and phenotype would not only benefit women with TS but could also contribute to the neurobiological understanding of the brain and its functional variations in general and for specific diseases and conditions.

10 Conclusions

Through various study designs and outcome measures, this thesis examined different aspects of the neurodevelopmental, psychiatric, cognitive, and social-emotional themes of the phenotype in women with TS. The results are at some points conflicting but also offers complementary information and deepen the overall understanding of women with TS.

To summarize the results, a higher likelihood of diagnoses of neurodevelopmental and psychiatric disorders was found in TS, but depression, anxiety and stress-related disorders were only seen elevated in the medical record review in adult woman with TS.

In adult women with TS, the uneven cognitive profile previously described, showed a clinically significant verbal >non-verbal split in the majority of the participating women, but no association between the IQ split and symptoms of ADHD or ASD was found.

Findings in reinforcement learning experiment indicate a different impact of social feedback in women with TS compared with controls.

Adult woman with TS experienced increased academic and social challenges during school age. The occupational and educational achievements were, however, the same as women in the general population in Sweden.

Comparing our findings between individuals grouped by maternal or paternal origin of the remaining X chromosome and karyotype have further offered complementary information about the relationship between genotype and phenotype.

In conclusion, although the overall findings in this thesis suggest indicate that women with TS face difficulties in various domains, when examining sociodemographic measures, our findings also show that educational achievements and employment rates do not differ when compared with the general population of women in Sweden.

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