Mental health and neurodevelopment in children and adolescents with Turner syndrome

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Abstract
Objectives: Turner syndrome (TS) is a rare sex chromosome aneuploidy, with an incidence of four in 10,000 new-born girls. TS is often associated with impaired social communication skills, but the extent to which these are attributable to Autism Spectrum Disorders (ASD) is uncertain. We made standardized assessments of the mental health and associated neurodevelopmental disorders in children and adolescents with TS and report on the prevalence of concurrent conditions.

Methods: Our sample comprised 127 girls with TS, 5–19 years of age. We obtained reports of their mental health from a combination of diagnostic interview (the Development and Wellbeing Assessment (DAWBA)), from the Strengths and Difficulties Questionnaire (SDQ) and from the Social Responsiveness Scale (SRS-2). Sources of information included parents, teachers and self-reports. The prevalence of mental health disorders in this sample was compared with age/sex matched national English data from typical controls.

Results: Most individuals with TS (83%) had experienced significant social communication difficulties and nearly one in four (23%) met diagnostic criteria for ASD on the DAWBA. One-third (34%) had at least one mental health or neurodevelopmental condition, and those girls with an ASD were at a greater risk of a co-occurring emotional disorder and/or attention deficit hyperactivity disorder (ADHD).

Conclusion: Children and adolescents with TS are substantially more likely to meet criteria for ASD than their typically developing peers. Our finding has clinical implications for appropriate behavioural management from preschool through to adolescence.

Keywords
autism, rare disorder, sex chromosome, turner syndrome, women’s health

Introduction
Turner syndrome (45, X; TS) is a common sex chromosome aneuploidy, with an incidence of 4 in 10,000 female births.¹ The physical phenotype is well-described; morbidities affect nearly every bodily system. These include dysmorphic features, skeletal abnormalities such as short stature, hearing difficulties, infertility, cardiac abnormalities, diabetes and thyroid problems.² However, relatively little research has been conducted on the psychological wellbeing of females with TS compared to studies of their physical health.³

Many women with TS experience lifelong difficulties in their social relationships,²,4,5 which are reminiscent of those experienced by people with an autism spectrum disorder (ASD). Both Creswel and Skuse⁶ and a recent Swedish patient registry study found an increased risk of clinically significant ASD in girls and women with TS.⁷
Traits of autism have also been documented by several investigations\textsuperscript{8−10} using tools such as the Autism Diagnostic Interview,\textsuperscript{6} the Childhood Autism Rating Scale\textsuperscript{11} and the Social Responsiveness Scale.\textsuperscript{5−10} Nonetheless, there is controversy about the basis of social difficulties associated with the syndrome, which some have attributed to excessively short stature, unusual physical appearance or social anxiety rather than a fundamental impairment in the processing of social cues.\textsuperscript{2,12} Obtaining a better understanding of autistic traits in TS is of clinical importance: there is increasing recognition that such traits are also often overlooked in typically developing girls and young women.\textsuperscript{13} The benefit of early identification of impaired social communication skills and the provision of appropriate management for ASD traits is well established.\textsuperscript{14} Early intervention is associated with gains in cognition, language and adaptive behaviour, as well as improvements in daily living skills and social behaviour.\textsuperscript{15}

Research into the most appropriate intervention to ameliorate social difficulties is viewed as a research priority by the TS community,\textsuperscript{3} yet no systematic assessment of psychosocial development in children has been made since 2001,\textsuperscript{16} and no survey of adult mental health since 2004.\textsuperscript{17} More recent studies have focused on specific problems such as attention deficit hyperactivity disorder (ADHD), depression or social anxiety but have lacked a comprehensive evaluation of risk in childhood or adulthood.\textsuperscript{5,18−24} A comprehensive and systematic evaluation of mental health and neurodevelopment in TS could lead to more effective and holistic care, enabling affected individuals to experience a better quality of life.

This study aimed to make a comprehensive evaluation of psychopathology, including neurodevelopmental conditions, associated with TS in girls and young women between 5 and 19 years. Our focus was primarily, but not exclusively, on the assessment of ASD traits. We employed a range of screening instruments, including a comprehensive diagnostic interview and a screening questionnaire for which we have comparison data on a representative sample of the general population. We used instruments that were employed in English national studies of young people’s mental health in 1999, 2004 and 2017.\textsuperscript{25−28} These were supplemented by standardized measures of autistic traits and social interaction difficulties, rated by parents, teachers and by self-report.

**Methods**

**Participants**

Participants included both children and adolescents with Turner Syndrome (confirmed by genetic reports or clinic letters) aged 5–19 years. They were either members of the UK Turner Syndrome Support Society or attended specialist National Health Service (NHS) clinics at University College London Hospital and Great Ormond Street Hospital. There were no additional exclusion criteria. In a subset of families, we obtained additional information from the child’s classroom teacher. All participated in the SOAR Study (SOcial skills And Relationships in Turner Syndrome) from September 2016 to November 2019.

We used normative comparison data collected as part of the English national surveys of child and adolescent mental health in 2004 and 2017.\textsuperscript{26,29,30} These data were accessed from NHS Digital and the UK Data Archive Service.\textsuperscript{29,30}

**Procedures**

This study employed a cross-sectional observational study design. Parents and young people above the age of 12 were invited to complete psychometric questionnaires online or in pen and paper form. If consent was obtained, teachers were contacted to complete psychometric questionnaires too. Ethical approval for the SOAR study was obtained through the University College London Ethics Committee and the NHS West London Research Ethics Committee (UCL REC: 11837/001; IRAS: 219817). Participants under the age of 16 were asked to sign an assent form and their parent or legal guardian signed an additional parent consent form. Young people aged 16 and over consented to take part on their own behalf and signed an adult consent form.

**Measures**

**Development and Wellbeing Assessment.** The Development and Wellbeing Assessment (DAWBA) is an online comprehensive interview with parents. It was used to collect information on the child’s behavioural adjustment and mental health, including friendships. The DAWBA has been used both in UK national and international surveys to assess child mental health in those aged between 5 and 19 years.\textsuperscript{25−28} Interpretation of DAWBA data was standardized, in accordance with DSM-5 diagnostic criteria. The assignment of DAWBA diagnoses has high inter-rater reliability in studies of typical children\textsuperscript{25,27,31,32} and in children with neurodevelopmental disorders.\textsuperscript{33} Clinical ratings in children attending a Social Communication Disorders Clinic have been validated against a comprehensive multidisciplinary assessment, using gold standard instruments, and it has been shown to have excellent sensitivity (93.3%) and specificity (78.6%).\textsuperscript{34} The Mental Health of Children and Young People in England 2017 survey data for girls aged 5 to 19 was used as a comparison sample. Descriptions of the cohort and sampling procedures are available from NHS Digital.\textsuperscript{30}

**Strengths and Difficulties Questionnaire.** The Strengths and Difficulties Questionnaire (SDQ) is a well-validated behavioural screening questionnaire.\textsuperscript{35} It includes subscales which measure emotional symptoms, conduct problems, hyperactivity, peer relationship problems and prosocial behaviour. Appropriate versions were completed online by
the parents and teachers, and self-reports were obtained from adolescents (Table 1). Subscales measuring emotional and behavioural problems can be combined to create a Total Difficulties score. An additional impact scale measures adjustment in daily life. SDQ data collected in the Mental Health of Children and Young People in Great Britain 2004 national study of girls aged 6 to 16 was obtained from the UK Data Service, and were used for comparison purposes.

Indices of Multiple Deprivation. Socioeconomic status was measured using postcode data using the Indices of Multiple Deprivation (IMD). IMD scores combine information from seven distinct domains to produce a relative deprivation rank. The domains include income, education, employment, crime, health, barriers to housing and services, and the living environment. IMD scores are ranked and organized into deciles; the first decile includes the most deprived areas and the 10th decile includes the least deprived areas.

Results

Participants
A total of 127 families consented to take part in the study; this included 127 parents (one per proband), 44 young people and 30 teachers. 37% of participants were recruited through specialist NHS Turner syndrome clinics (n = 47) and 63% of families were recruited from the UK Turner Syndrome Support Society (n = 80). The distribution of socioeconomic status of the participants, as measured by IMD scores, was skewed towards relatively less deprived centiles (deciles 1–5 = 34%; deciles 6–10 = 66%). 78.7% of parents completed the DAWBA (n = 100), 75.6% completed the SDQ (n = 96) and 81.9% completed the SRS-2 (n = 104). 75% of eligible young people contributed by answering a self-report questionnaire (n = 33) and 30 teachers returned at least one completed questionnaire.

Participants themselves approached teachers about taking part; therefore, the number of teachers who declined is not known.

Table 1. Prevalence of DAWBA diagnoses: UK national study of typically developing (TD) girls and girls with TS.

| Disorder prevalence (%) | TS girls n = 100 | TD girls n = 3,803 | RR | TS with DAWBA ASD n = 23 | TS without DAWBA ASD n = 77 | RR |
|-------------------------|------------------|-------------------|----|-------------------------|-----------------------------|----|
| Any disorder            | 34               | 12.9              | 2.64 | –                       | –                           | –  |
| Emotional disorders     | 13               | 10                | 1.3  | 26.1                    | 9.1                         | 2.9 |
| Anxiety disorders       |                  |                   |      |                         |                             |    |
| Separation anxiety disorder | 2             | 0.6               | 3.33 | 0                       | 2.6                         | 0  |
| Generalized anxiety disorder | 7             | 1.8               | 3.88 | 21.8                    | 2.6                         | 8.4|
| Obsessive compulsive disorder | 1          | 0.4               | 2.5  | 0                       | 1.3                         | 0  |
| Specific phobia         | 3                | 0.9               | 3.33 | 4.3                     | 2.6                         | 1.7|
| Social phobia           | 2                | 1.1               | 1.82 | 0                       | 2.6                         | 0  |
| Depressive disorders    |                  |                   |      |                         |                             |    |
| Major depressive episode | 1              | 2.8               | 0.36 | 4.3                     | 0                           | –  |
| Attention deficit hyperactivity disorder (ADHD) | 13 | 0.6 | 21.6 | 39.1 | 5.2% | 7.5 |
| Autism spectrum disorder (ASD) | 23 | 0.4 | 57.5 | 100 | 0 | – |
| Eating disorders        | 1                | 0.7               | 1.43 | 0                       | 1.3                         | 0  |
| Tics/other less common disorders | 2 | 0.6 | 3.33 | 8.7 | 0 | – |

TS: Turner Syndrome; TD: Typically Developing; RR: Relative Risk; DAWBA: Development and Wellbeing Assessment.
The sample comprised a wide range of TS karyotypes, which were representative of the TS population (Supplemental Table S1). We were not able to verify the karyotype of 18 participants. Data from participants with unconfirmed karyotypes were included in the final analysis as they obtained a similar range of scores on the SDQ and SRS-2, and their DAWBA profiles were also comparable to those of the remaining sample.

Mean participant age was 12.1 years (SD = 4.4). By late adolescence, all were taking oestrogen replacement therapy, which was instituted at a mean age of 13 years (SD = 2.0) and which was associated with menarche at a mean age of 14.8 years (SD = 2.6). 10.4% of participants had a severe hearing impairment and 4.2% had a severe visual impairment. Girls of school age were usually in mainstream school 93% (N = 94); of these, 42% received additional educational support and 3% were in a special unit. The remaining 7% attended a special needs school.

**Mental health**

The prevalence of mental health and neurodevelopmental disorders was assessed using the DAWBA parental interview. 34% of participants met diagnostic criteria for at least one mental health disorder of clinical significance, a relative risk 2.6 times greater than typically developing girls (Table 1). 13% met criteria for an anxiety disorder and 1% met criteria for depression. None of the participants met criteria for a behavioural disorder. The proportion of participants with neurodevelopmental disorders was substantially higher than would be expected compared to female population norms. In the TS group, 13% met criteria for ADHD and 23% of participants met diagnostic criteria for an ASD. This is equivalent to a relative risk (RR) of 21.6 for ADHD and 57.5 for ASD compared to typically developing girls.

Of those with a mental health disorder (n = 34), 59% had more than one type of disorder (n = 20) and 40% had two or more types of disorder (n = 14; Figure 1). Girls who met criteria for an ASD were at an increased risk in comparison to others with TS of both an associated emotional disorder (RR 2.9) and ADHD (RR 7.5; Table 2).

**Autistic traits and friendships**

The SRS-2 measures several domains of autistic behaviour and provides an overall likelihood score (Table 2). Only 39% of TS participants scored in the ‘normal’ range. 32.6% scored in the ‘mild’ and ‘moderate’ ranges and 28% scored in the ‘severe’ range, which indicates a strong probability of a clinical diagnoses of an ASD. Overall, nearly two-thirds (61%) had autistic-like characteristics in their social interactions by parental report (Table 2). The SRS-2 scores from teachers were similar to those provided by parents (Table 2).

**Discussion**

This investigation is the largest to have been conducted into the mental health of young people with TS, using standardized instruments. We found that they experienced higher rates of psychiatric and social skills difficulties than age-matched girls from the general population. A third of participants met criteria for a mental health disorder; rates of neurodevelopmental disorders, anxiety, eating disorders and tic disorders were high relative to national data. The prevalence of depression was lower than in comparison girls from the general population at all ages (relative risk 0.35),
consistent with previous reports of TS-related depression in childhood and adolescence.\textsuperscript{16,20,21}

Parental reports obtained from the DAWBA and the SRS-2 indicated that approximately one in five girls met criteria for an ASD. This is equivalent to a 57-fold relative risk of meeting criteria for an ASD in TS compared to typically developing girls. There is undoubtedly a strong association between TS and risk of ASD, despite earlier claims to the contrary.\textsuperscript{2} Most participants (61%) were reported to have mild to moderate autistic traits, which had a clinically significant impact on their day-to-day social interaction. The SRS-2 profile was consistent with previous research using the SRS-1 on a smaller sample of girls with TS.\textsuperscript{9} TS girls who met criteria for ASD were also more likely to meet criteria for anxiety and/or ADHD. This is consistent with previous reports of co-occurring conditions in girls and young women with ASD without intellectual disabilities.\textsuperscript{40,41}

Table 2. SRS-2 scores by informant (5–19 years).

| SRS-2 total score | TS Parent N=104 | TS Teacher N=26 | TD Parent N=1,896 |
|-------------------|-----------------|-----------------|-------------------|
| Normal            | 39.4%           | 42.3%           | 84.1%             |
| Mild              | 16.3%           | 26.9%           | 9.2%              |
| Moderate          | 16.3%           | 7.7%            | 6.1%              |
| Severe            | 27.9%           | 23.1%           | 0.6%              |

SRS-2 Scales, M (SD) | TS Parent N=104 | TS Teacher N=26 |
|---------------------|-----------------|-----------------|
| Social awareness    | 62.8 (14.0)     | 58.9 (13.9)     |
| Social cognition    | 63.4 (16.3)     | 58.0 (13.7)     |
| Social communication| 64.4 (15.1)     | 61.1 (12.7)     |
| Social motivation   | 62.4 (13.8)     | 59.1 (12.2)     |
| Restricted interests and repetitive behaviour | 67.2 (15.7) | 67.9 (21.7) |
| Total score         | 66.0 (15.2)     | 62.4 (14.3)     |

SRS: Social Responsiveness Scale; TS: Turner Syndrome; TD: Typically Developing.

Table 3. DAWBA social communication and friendship data: Friendship and peer difficulties in TS.

| Instrument                                      | TS Parent | TD Parent | TS Teacher | TS Self-report |
|-------------------------------------------------|-----------|-----------|------------|----------------|
| SDQ Peer difficulties scale, %                  | N=96      | N=5,145   | N=30       | N=33           |
|                                                  | 5 to 16 years | 5 to 16 years | 5 to 19 years | 5 to 19 years |
| Normal                                          | 31.3%     | 79.8%     | 71.4%      | 75%            |
| Slightly raised                                 | 8.3%      | 10.1%     | 10.7%      | 20.9%          |
| High–very high                                  | 60.4%     | 10.1%     | 17.9%      | 4.1%           |
| DAWBA Friendship, %                             | N=88      | N=3,798   |            |                |
| How easy does your daughter find it to make friends? |           |           |            |                |
| Harder than average                             | 71.6%     | 9.1%      |            |                |
| About average                                   | 20.5%     | 35.1%     |            |                |
| Easier than average                             | 8%        | 55.8%     |            |                |
| How easy does your daughter find it to keep friends? |           |           |            |                |
| Harder than average                             | 55.7%     | 5%        |            |                |
| About average                                   | 40.9%     | 35.7%     |            |                |
| Easier than average                             | 3.4%      | 59.3%     |            |                |
| How many friends does she fairly often spend time with? |        |           |            |                |
| None                                            | 17%       | 1.2%      |            |                |
| One                                             | 18.2%     | 4.2%      |            |                |
| Two to four                                     | 64.8%     | 43%       |            |                |
| Five to nine                                    | 0         | 40.3%     |            |                |
| 10 or more                                      | 0         | 11%       |            |                |

TS: Turner Syndrome; TD: Typically Developing; SDQ: Strength and Difficulties Questionnaire; DAWBA: Development and Wellbeing Assessment.
By parental report nearly three-quarters (71.6%) did not make friends easily and most had fewer friends than typically developing female peers. An important observation, consistent with previous reports, is that young people with TS did not themselves report any peer difficulties. Teachers also reported fewer peer interaction difficulties than parents. This is consistent with the observation that young women with ASD but normal-range intelligence are often overlooked in the classroom, because they do not cause any problems but tend to be withdrawn. Subtle social communication issues with peers can be difficult to detect in a classroom setting. There are a number of possible explanations for the discrepancy between young people and parent’s accounts of socialization. We have consistently found a strong social-desirability bias in self-reports of social behaviour, during the course of previous TS investigations together with a lack of social insight. We assume these young people are reporting their desired rather than their actual experience of socialization, although there is an additional possibility that they are satisfied with fewer friendships than typical females of similar age.

Despite the genetic heterogeneity of karyotypes of participants in our study (monosomy, ring, partial deletion, etc.), the social communication phenotype was remarkably homogeneous. A number of different genomic theories have been proposed to account for the social skills difficulties and high rates of ASD in this condition. For instance, in typical females the second X-chromosome could act as a protective factor increasing the threshold at which autistic traits are expressed. However, most sex chromosome aneuploidies are associated with an increased prevalence of ASD including 47,XYY syndrome (~19%–36% ASD), Klinefelter syndrome (XXY, ~11%–27% ASD), 48,XXYY syndrome (~28%–35% ASD), although possibly not in trisomy X syndrome. The risk of expressing autistic traits in TS could be influenced by an epigenetic imprinting effect. Previous research has indicated that X-monosomic TS girls those whose single X was inherited from their mothers (~80%, Xm) had more severe social communication difficulties that those who had inherited their X from their fathers (Xp). We did not have any information on the parental origin of the intact X-chromosome in this sample. Recent research from observation paradigms in social gaze impairments and from neuroimaging studies on brain development trajectories support imprinting effects, as do studies of X-monosomic mice.

**Strengths and limitations**

Previous equivalent studies have not only been smaller in scale but were also less comprehensive in scope than this investigation. They focused exclusively on adolescents (n = 122), or adult women (n = 100) and did not discuss the neurodevelopmental characteristics of TS. A limitation of this investigation is that we did not have the opportunity to meet our participants face to face, to make our own observations, but we relied largely upon online parental reports. The interview we employed, the DAWBA, is not a clinical diagnostic assessment. Formal psychiatric diagnoses require face-to-face clinical interviews and observations. Although it is possible that the rates of TS have been inflated, this is unlikely as the ASD module has been validated against multidisciplinary face-to-face clinical assessment and was used in three national studies of children’s mental health in the United Kingdom. Furthermore, the DAWBA is a more conservative measure of autism than the SRS-2. Only 54% of participants with scores in the severe range on the SRS-2 obtained a diagnosis of autism on the DAWBA (kappa = 0.21, p < .001).

Future studies will need to include child and adolescents self-reports, as well as investigate the discrepancies between them. Our study used normative data rather than recruiting a control participants. Future studies would benefit from recruiting participants matched for adaptive function and processing speed ability, as this is known to be different in TS. This study, like all studies of rare genetic disorders, may be affected by an ascertainment bias. Families needed to be engaged with their clinical services or the UK support society to find out about the study. It is also possible that the study adverts attracted more families who have children experiencing psychological difficulties than those without difficulties.

**Conclusion**

Taking a systematic approach to assessing mental health and neurodevelopment has revealed high rates of social skills difficulties, mental health disorders (anxiety disorders) and neurodevelopmental disorders (ASD and ADHD) in girls and young women with TS. The rates of co-occurring disorders were substantially higher in those that met criteria for an ASD. Clinicians managing the care of children with TS should consider referrals for ASD assessment, in order to facilitate the implementation of social skills support, as these have been shown to be effective in young women with TS.

**Declarations**

**Ethics approval and consent to participate**

Ethical approval for the SOAR study was obtained through the University College London Ethics Committee and the NHS West London Research Ethics Committee (UCL REC: 11837/001; IRAS: 219817). A written informed consent was obtained from all participants before enrolling in the study.

**Consent for publication**

Participants provided consent for use of their data in publication.

**Author contribution(s)**

Jeanne Wolstencroft: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.
William Mandy: Conceptualization; Supervision; Writing – review & editing.
David Skuse: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing – review & editing.

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The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials
The anonymous data used and analysed in this study is available from the corresponding author upon reasonable request.

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Supplemental material
Supplemental material for this article is available online.

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