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Anxiety in Turner syndrome: Engaging community to address barriers and facilitators to diagnosis and care

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Abstract

Turner syndrome (TS), caused by complete or partial loss of the second sex chromosome, is associated with complex medical manifestations. The TS community identifies anxiety as a major contributor to reduced quality of life. The study aimed to improve understanding of anxiety symptomatology, diagnosis, and care in individuals with TS. A mixed methods design integrated community engagement, including community leaders as co-investigators and a community advisory board, an online survey ($N = 135$), and in-depth interviews ($N = 10$). The majority of respondents reported that anxiety symptoms occur two or more days per week, with self-advocates reporting more frequent symptoms than caregivers ($p = 0.03$). Self-advocates reported feeling anxious more often at school/work; both rater groups reported anxiety-related behaviors were most likely to be expressed at home. Insomnia was the most common symptom of anxiety endorsed across age and rater groups (>70%). Anxiety symptoms and triggers changed with age and often were undiagnosed or untreated during childhood. Therapy and medication were reported as helpful by most respondents who had tried these strategies. Qualitative themes included: 'Triggers for anxiety are related to TS', 'Anxiety impacts the whole family', and 'Opportunities for early identification and intervention'.

KEYWORDS
anxiety, community-based participatory research, mental health, monosomy X, psychology, Turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is a rare genetic disorder characterized by a missing or incomplete second sex chromosome with wide phenotypic and genotypic heterogeneity (Gravholt et al., 2017). TS often results in multisystem, complex medical manifestations, including short stature, premature ovarian failure, autoimmune disorders, cardiovascular disease, social vulnerabilities, and neurocognitive deficits (Gravholt et al., 2017). In addition to this constellation of manifestations, the TS community emphasizes that anxiety highly impacts quality of life. While clinical experts agree that individuals with TS are at greater risk for neurocognitive and psychological issues, data on these conditions are inconsistent. Neurocognitive conditions that are well-documented to be associated with TS include learning disabilities (Kremen et al., 2023), attention deficit hyperactivity disorder (ADHD; Russell et al., 2006), and autism spectrum disorder (ASD; Björlin Avdic et al., 2021; Wolstencroft et al., 2020). Multiple studies have shown that individuals with TS have increased risk for anxiety compared with the general population, although symptoms appear more notable during adolescence and adulthood (Cardoso et al., 2004; Kiliç

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et al., 2005). A large-scale chart review has shown only 17% of pediatric patients with TS have a diagnosed anxiety disorder (Kremen et al., 2023), similar to a prevalence of 18% in the general pediatric population (Kessler et al., 2005).

Despite this inconsistent evidence, patients and families affected by TS report anxiety is a critical area of concern. When asked about priorities for research, 84% of women with TS and 91% of parents report that research on emotional/behavior problems is very important (Sandberg et al., 2019). Although there are multiple possible reasons for the incongruency within the literature, including underdiagnosis of anxiety in TS due to inadequate screening (Davis et al., 2020), lack of recognition of behavioral symptoms as indicative of anxiety, or insufficient mental health referral resources, the underlying barriers and facilitators to care for anxiety in TS are largely unknown.

This study utilized a mixed-methods and Community-Based Participatory Research (CBPR) approach, which equitably involves community partners in all aspects of the research process (Israel et al., 1998). The study team partnered with patients with TS, parents of individuals with TS, and clinicians specializing in healthcare for individuals with TS to achieve the following aims: (1) to quantify the symptoms, triggers, and solutions for anxiety in TS and to evaluate any differences by age or reporter (caregiver vs. self-advocate) and (2) to describe the subjective experiences of anxiety in youth and young adults with TS including treatment experiences, barriers to care, and impact on quality of life.

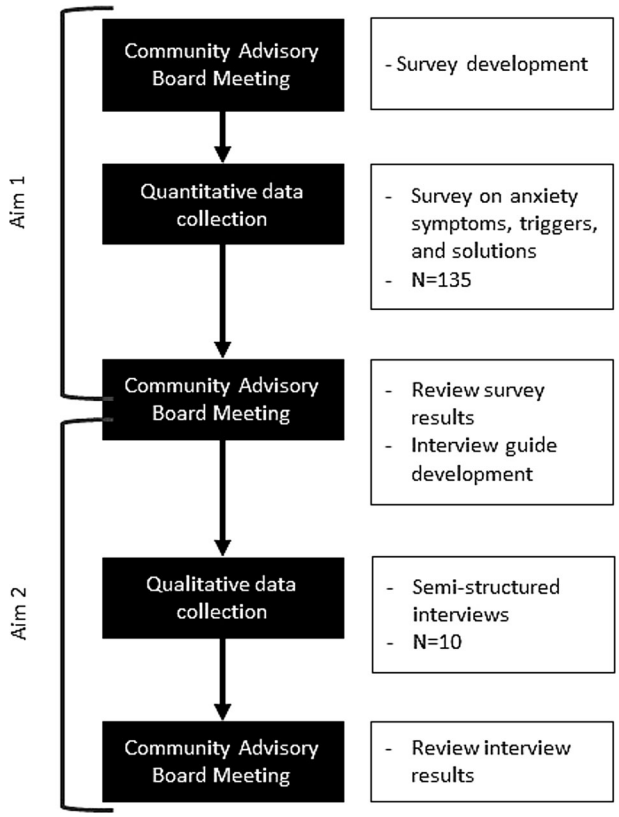

FIGURE 1 Timeline of the methodology employed for both aims, depicting sequential explanatory mixed-methodology and community engagement utilized throughout.

2 | MATERIALS AND METHODS

2.1 | Participant recruitment

Individuals with TS (referred to henceforth as self-advocates) and caregivers of individuals with TS (referred to henceforth as caregivers) participated in this study. A community advisory board (CAB) comprised of four caregivers, three self-advocates, and two clinicians who specialize in TS met periodically to determine study priorities and interpret results (Figure 1). Self-advocates had to have a TS diagnosis, including being assigned female at birth, but gender identity was not an inclusion/exclusion criterion. For aim 1, self-advocate participants had to be 10-years or older and for aim 2, 12-years or older. For both aims, caregiver participants' children were 3-years or older. Recruitment occurred via the INSIGHTS Registry (Kanakatti Shankar et al., 2024), national support group Facebook pages, and at TS multidisciplinary clinic visits at a large pediatric center. Participants self-reported diagnosis of TS for aim 1, and study team members confirmed diagnosis via medical record review for aim 2.

2.1.1 | Editorial policies and ethical considerations

The Colorado Multiple Institutional Review Board reviewed and approved this study (COMIRB #22-0550). The study team obtained informed consent from participants over 18-years of age, and assent from participants younger than 18 years along with parental consent.

2.2 | Partnership formation

This project was a formal partnership between the eXtraOrdinary Kids Multidisciplinary Turner Syndrome Clinic and Research Team and Turner Syndrome Colorado (TSCO), a community-based non-profit organization that aims to connect patients with TS and their families with the broader TS community and support local resources for TS. TSCO serves patients and families in the state by supporting the TS multidisciplinary clinic and hosting social and educational events. TSCO is run entirely by patients with TS and their families. This organization began in 2010 with the goal of establishing a local multidisciplinary clinic for TS.

2.3 | Study design

The current study used a mixed methods sequential explanatory design (Fetters et al., 2013). A cross-sectional survey that was designed and modified by the CAB inclusive of anxiety symptoms, triggers, and solutions was disseminated to individuals with TS and

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caregivers to evaluate aim 1. Clinical experts on the CAB provided expertise in DSM-5 criteria and their clinical experience with diagnosing and treating anxiety in TS. Survey results and CAB input informed a subsequent qualitative phase where a subset of participants completed semi-structured interviews to evaluate aim 2 (Figure 1).

2.4 | Quantitative procedures

Eligible participants were recruited from July through October 2022. Participants completed a survey, available in English and Spanish, asking about anxiety symptoms, triggers, and solutions along with demographic information. Surveys were completed independently in clinic or at home using the online REDCap platform (Harris et al., 2009). Self-advocates and caregivers could complete the survey independently and each participant received a $15 gift card upon survey completion.

2.4.1 | Measures

The demographic questionnaire was comprised of 10 items assessing race, age, education level, socioeconomic status (measured by annual income), relationship status, karyotype, age of TS diagnosis, and diagnosed comorbid psychological disorders. Self-advocates reported their own demographics while caregivers reported on both their child with TS and their own demographics. Questions on the anxiety survey for caregivers and self-advocates were nearly identical with slight change of wording to reflect participant role.

Participants then completed the anxiety survey where they were asked to report on how many days per week anxiety is experienced/expressed and where anxiety is most likely to be experienced/expressed. The impact of anxiety on the ability to function in daily life was measured with a scaled item from 0 to 10, where 0 represented anxiety not impacting activities of daily life, 5 represented anxiety impacting daily life regularly but still able to participate in daily activities, and 10 represented anxiety impacts daily life most of the time and impedes the ability to participate in daily activities. Frequencies of 20 cognitive/behavioral symptoms and 15 physical symptoms of anxiety (Figure 3, Table A1) were measured with a Likert scale ranging from never, defined as "not displaying the symptom at all," to often or always, defined as "displaying the symptoms multiple times per week." Survey items measuring symptoms of anxiety were adapted for the TS community from an existing community-engaged survey used in another rare genetic condition (Lozano et al., 2022) with a goal of capturing (1) observable behaviors that others might attribute to anxiety, (2) internal experiences that may not be apparent to others, (3) common DSM-5 diagnostic criteria for anxiety, and (4) behaviors reported by the CAB as being present in TS. To evaluate triggers for anxiety, participants rated the likelihood of 19 potential events to trigger anxiety (Table B1) from extremely unlikely (0) to extremely likely (4). To determine strategies helpful in reducing anxiety, participants reported on 15 potential strategies (Table 2), stating if they had tried the strategy, and if so, rating it from never helpful to almost always helpful. All symptoms, triggers, and strategies included in the survey were developed in collaboration with the CAB, based on stakeholder lived experiences, and clinician experience and expertise. A draft of the survey was piloted with CAB members and other parents of children with TS to test face validity, feasibility, and question comprehension. Definitions were added into the survey for any terms that were unclear (i.e., rumination was defined as "Experiencing repetitive negative thought loops and not letting them go, being hard on oneself"). The final version of survey was checked, refined, and approved by the CAB prior to study enrollment.

2.4.2 | Statistical analysis

Caregivers and self-advocates were stratified into age groups and descriptive statistics were used to summarize results. A linear mixed model fit by maximum likelihood adjusting for age (13+) and random intercept for subject was used to compare caregivers and self-advocates across frequency of anxiety symptoms and impact on daily life scale. Ordinal logistic regression was performed to examine the relationship between age and Likert scale variables. A generalized linear model for negative binomial distributed data was fit for number of evidence-based anxiety interventions (daily or as-needed medications, therapy), adjusting for income and education level. Age group differences were analyzed to evaluate non-linear relationships between age and symptoms/triggers. Age group brackets were determined by the CAB, including input from TS clinicians, parents, and patient advocates to ensure meaningful analyses. Age groups differed between respondent groups based on eligibility criteria and the number of respondents (e.g., self-advocate inclusion criteria were ages 10+, few adults were represented in the caregiver respondent group). Caregiver respondents were divided into early childhood (3–5 years), middle childhood (6–12 years), adolescence (13–17 years), and adults (18+). Self-advocate respondents were divided into middle childhood (10–12 years), adolescence (13–17 years), young adults (18–29 years), and older adults (30+ years). A Fisher's exact test with Monte Carlo simulation was used to test difference between age groups for outcomes. All statistical analyses were performed in R (v 4.2.1).

2.5 | Qualitative procedures

Eligible participants were recruited from October 2022 through January 2023. Participants completed the online survey first and were then asked to complete a 60-min interview via Zoom (Archibald et al., 2019) regarding their or their child's anxiety experience. Participants were purposively sampled from the survey respondents based on our CAB feedback to include a range of ages, moderate to high anxiety impact scores, and endorsed sleeping problems. Interviews were conducted by study team members trained in qualitative data collection who ensured the participant was in a comfortable and private space. Self-advocates and caregivers had the option to complete

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the interview as a parent–child dyad or independently and each participant received a $35 gift card.

2.5.1 | Interview guide

The study team and CAB collaborated to develop the interview guide based on survey results and CAB priorities. The semi-structured guide focused on participants' subjective experiences with anxiety, including anxiety symptoms, the impact of anxiety on daily life, and barriers and facilitators to care. Specific questions about conversations with healthcare providers and sleep-related symptoms were included to expand upon survey results.

2.5.2 | Qualitative analysis

Interviews were audio recorded and transcribed via Zoom (Zoom Video Communications Inc., 2016). Research team members partnered with three CAB members, including a clinical expert in TS and two caregivers, to conduct a team-based qualitative rapid analysis of interview data (Gale et al., 2019). First, the analysis team developed a templated summary table based on predetermined domains prioritized during the initial CAB meetings (e.g., triggers for anxiety, signs and symptoms of anxiety, solutions, and barriers to care). Analysis team members read two transcripts (one self-advocate, one caregiver) separately, extracting raw data (illustrative quotes) from the transcripts and summarizing key points under each predetermined category. Team members also extracted data and summarized key points for any emergent themes that were not included in the templated summary tables. Next, the analysis team met to review a merged summary table, comparing selected quotes and key points from each member. The team discussed any differences in interpretation of the data and all emergent themes, resulting in development of a final consensus summary table for each transcript. Two research team members with qualitative research expertise then summarized the remaining eight transcripts (four each) into summary tables. Summary tables were consolidated by participant group (caregivers, self-advocates) to identify common themes and illustrative quotes within and between groups. Preliminary themes were presented to the CAB for in-depth discussion, refinement, and clarification.

2.6 | Mixed methods procedures

Quantitative survey results were synthesized by the CAB to inform sampling priorities and data collection in the qualitative phase. The sampling framework was developed based on key survey findings and the interview guide was developed to expand and explain specific survey results of interest to the CAB. Methodological triangulation between statistical results and qualitative themes (Bekhet & Zauszniewski, 2012) was used to increase validity and enhance our understanding of anxiety in TS to develop key overarching findings.

3 | RESULTS

3.1 | Participant demographics

A total of 135 participants (61 caregivers and 74 self-advocates) completed the survey (Table 1). Self-advocate participants were 25.7 ± 12.1 years old with a range from 10 to 64 years. Caregiver participants' children were 11.9 ± 6.4 years old with a range from 3 to 31 years. Most respondents were non-Hispanic and female-identifying. Reported psychological diagnoses were common in both respondent groups; only 31% of self-advocates and 23% of caregiver respondents reported no clinical psychological diagnosis. The most common diagnoses were anxiety disorders with 77% of self-advocates and 61% of caregiver's children.

Five caregivers and five self-advocates completed interviews. The 10 interview participants were all non-Hispanic white, female-identifying, and represented ages ranging from 12 to 22 for self-advocates and from 7 to 16 years for caregivers' children.

3.2 | Quantitative results

Most respondents reported anxiety symptoms were expressed/experienced two or more days per week, and both caregivers and self-advocates reported that anxiety regularly impacts daily life (mean of 4.2 and 5.1 out of 10 respectively). Self-advocate respondents reported higher frequency of anxiety symptoms than caregiver respondents (OR 4.7, 95%CI 1.2–19.3; Figure 2). There were no significant differences in the impact of anxiety on daily life as reported by caregivers compared to self-advocates ($p = 0.88$). Frequency of caregiver reported anxiety symptoms increased with the age of the child with TS; each year increase in age was associated with a 10% increase in odds of being more impacted by anxiety. A significant association was not found for the self-advocate report. Self-advocates reported *feeling* anxious most often at school/work (71%), while both caregivers and self-advocates reported anxiety-related behaviors were most likely to be *expressed* at home (61% and 78%, respectively).

3.2.1 | Symptoms of anxiety

The top behavioral symptoms of anxiety reported by caregivers were facial change (73.7%), clinging (64.9%), avoidance (64.9%), and rumination (64.9%). The top behavioral symptoms reported by self-advocates were rumination (85.7%), avoidance (82.9%), fidgeting (82.9%), and negative thoughts/speech, including negative self-talk (81.4%). The top physical symptoms reported by caregivers and self-advocates were the same: insomnia (63.2% and 81.4%, respectively), body tension (45.6% and 67.1%, respectively), zoning out (42.1% and 62.9%, respectively), and increased heart rate (36.8% and 70.0%, respectively.

Some behavioral and physical symptoms of anxiety showed a significant linear relationship with age. Per caregiver report, physical

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TABLE 1 Sociodemographic characteristics of survey participants.

Characteristic	Self-advocates ($n = 74$) *n* (%)	Caregiver participants ($n = 61$) *n* (%)	Caregiver participants' child *n* (%)
Age (mean ± SD)	25.7 ± 12.1	Not applicable	12.0 ± 6.4
Race			
American Indian/Alaska Native	2 (2.7%)	2 (3.3%)	2 (3.3%)
Asian	2 (2.7%)	0 (0.0%)	0 (0.0%)
Black or African American	4 (5.4%)	2 (3.3%)	5 (8.2%)
White	62 (83.8%)	56 (91.8%)	52 (85.2%)
Other	4 (5.4%)	1 (1.6%)	1 (1.6%)
Unknown or not reported	0 (0.0%)	0 (0.0%)	1 (1.6%)
Ethnicity			
Hispanic or Latinx	6 (8.1%)	6 (9.8%)	7 (11.5%)
Non-Hispanic or Latinx	58 (78.4%)	54 (88.5%)	53 (86.9%)
Other	7 (9.5%)	1 (1.6%)	0 (0.0%)
Unknown or not reported	3 (4.1%)	0 (0.0%)	1 (1.6%)
Gender identity			
Female/woman	70 (94.6%)	56 (91.8%)	70 (94.6%)
Male/man	1 (1.4%)	4 (6.6%)	1 (1.4%)
Gender fluid/non-binary	2 (2.7%)	0 (0.0%)	2 (2.7%)
Transgender	0 (0.0%)	1 (1.6%)	0 (0.0%)
Unknown or not reported	1 (1.4%)	0 (0.0%)	1 (1.4%)
Education level			
9th grade or less	15 (20.3%)	0 (0.0%)	Not applicable
Partial HS no diploma	8 (10.8%)	0 (0.0%)	
High school degree	4 (5.4%)	6 (9.8%)	
Partial college	8 (10.8%)	8 (13.1%)	
Standard college/university degree	27 (36.5%)	22 (36.1%)	
Graduate/professional degree	10 (13.5%)	24 (39.3%)	
Unknown or not reported	2 (2.7%)	1 (1.6%)	
Relationship status			
Single	50 (67.6%)	8 (13.1%)	Not applicable
Married	18 (24.3%)	45 (73.8%)	
Divorced	2 (2.7%)	3 (4.8%)	
Other	4 (5.4%)	4 (6.6%)	
Unknown or not reported	0 (0.0%)	1 (1.6%)	
Region of current residence			
Midwest	12 (16.2%)	8 (13.1%)	8 (13.1%)
Northeast	5 (6.8%)	4 (6.6%)	4 (6.6%)
South	13 (17.6%)	16 (26.2%)	16 (26.2%)
West	31 (41.9%)	32 (52.5%)	31 (50.8%)
Unknown or not reported	13 (17.6%)	1 (1.6%)	2 (3.3%)
Timing of Turner syndrome diagnosis			
Prenatal	10 (13.5%)	Not applicable	23 (37.7%)
First year of life	14 (18.9%)		21 (34.4%)
Early childhood (1–5 years)	10 (13.5%)		7 (11.5%)
Late childhood (6–12 years)	19 (25.7%)		8 (13.1%)
Adolescence (13–19 years)	13 (17.6%)		2 (3.3%)

(Continues)

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TABLE 1 (Continued)

Characteristic	Self-advocates ($n = 74$) *n* (%)	Caregiver participants ($n = 61$) *n* (%)	Caregiver participants' child *n* (%)
Adulthood (19+ years)	5 (6.8%)		0 (0.0%)
Unknown or not reported	3 (4.1%)		0 (0.0%)
Psychological diagnoses			
Any anxiety disorder	57 (77.0%)	Not applicable	37 (60.1%)
Generalized anxiety disorder	32 (43.2%)		16 (26.2%)
Social anxiety disorder	12 (16.2%)		7 (11.4%)
Panic disorder	5 (6.8%)		4 (6.6%)
Anxiety unspecified/other	5 (6.8%)		9 (14.8%)
Agoraphobia	2 (2.7%)		1 (1.6%)
Selective mutism	1 (1.4%)		0 (0.0%)
Obsessive compulsive disorder	10 (13.5%)		5 (8.2%)
Adjustment disorder	3 (4.1%)		1 (1.6%)
Major depressive disorder	10 (13.5%)		0 (0.0%)
Unspecified depression	9 (12.2%)		5 (8.2%)
ADHD	8 (10.8%)		18 (29.5%)
Developmental delay	3 (4.1%)		15 (24.6%)
Specific learning disorder	10 (13.5%)		9 (14.8%)
Nonverbal learning disorder[a]	15 (20.3%)		9 (14.8%)
Intellectual disability	1 (1.0%)		7 (11.5%)
Autism spectrum disorder	3 (4.1%)		8 (13.1%)
None	23 (31.1%)		14 (23.0%)

[a]Nonverbal learning disorder is not currently a recognized diagnosis in the DSM, however, many families with TS have identified this diagnosis as a helpful label in understanding their child. All diagnoses in the above table are self-reported by the survey respondent.

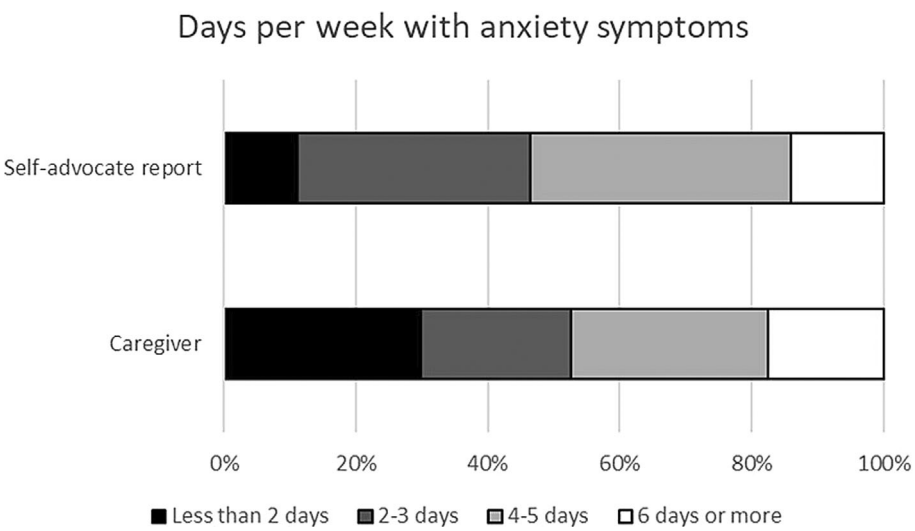

FIGURE 2 Reported days per week where anxiety symptoms are felt or observed within each reporter group. Self-advocate respondents reported a statistically significantly higher frequency of anxiety symptoms than caregiver respondents ($p = 0.03$).

aggression (OR: 0.91, 95%CI: 0.83–0.99, $p = 0.02$) and crying/tantrums (OR: 0.90, 95%CI: 0.83–0.97, $p = 0.01$) as symptoms of anxiety decreased with age. Per self-advocate report, clinging (OR: 0.96, 95%CI: 0.92–0.99, $p = 0.02$) and diarrhea (OR: 1.07, 95%CI: 1.03–1.12, $p = 0.001$) decreased with age, while body tension (OR: 1.04, 95%CI: 1.01–1.08, $p = 0.01$) increased with age.

Behavioral and physical symptoms of anxiety were also analyzed by age groups; frequencies and *p*-values for group differences are reported in Table A2 and represented visually in Figure 3. Significant differences in symptoms identified between age groups were consistent with linear relationships identified above (physical aggression higher in younger children ($p = 0.04$), body tension higher in adults

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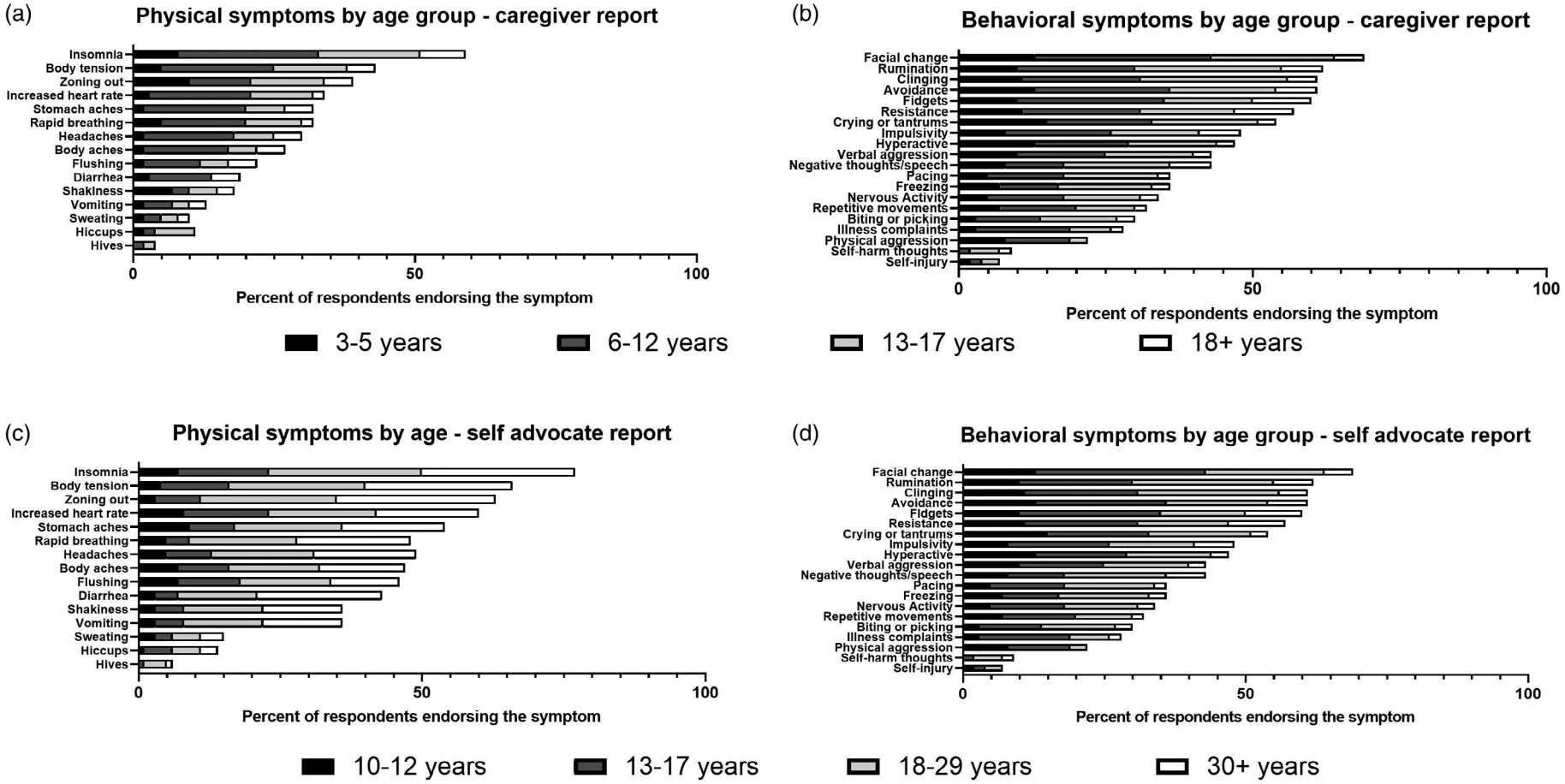

FIGURE 3 Reported symptoms of anxiety endorsed (responded with sometimes, often, or almost always) by each reporter group, broken down by age category. *$p < 0.05$.

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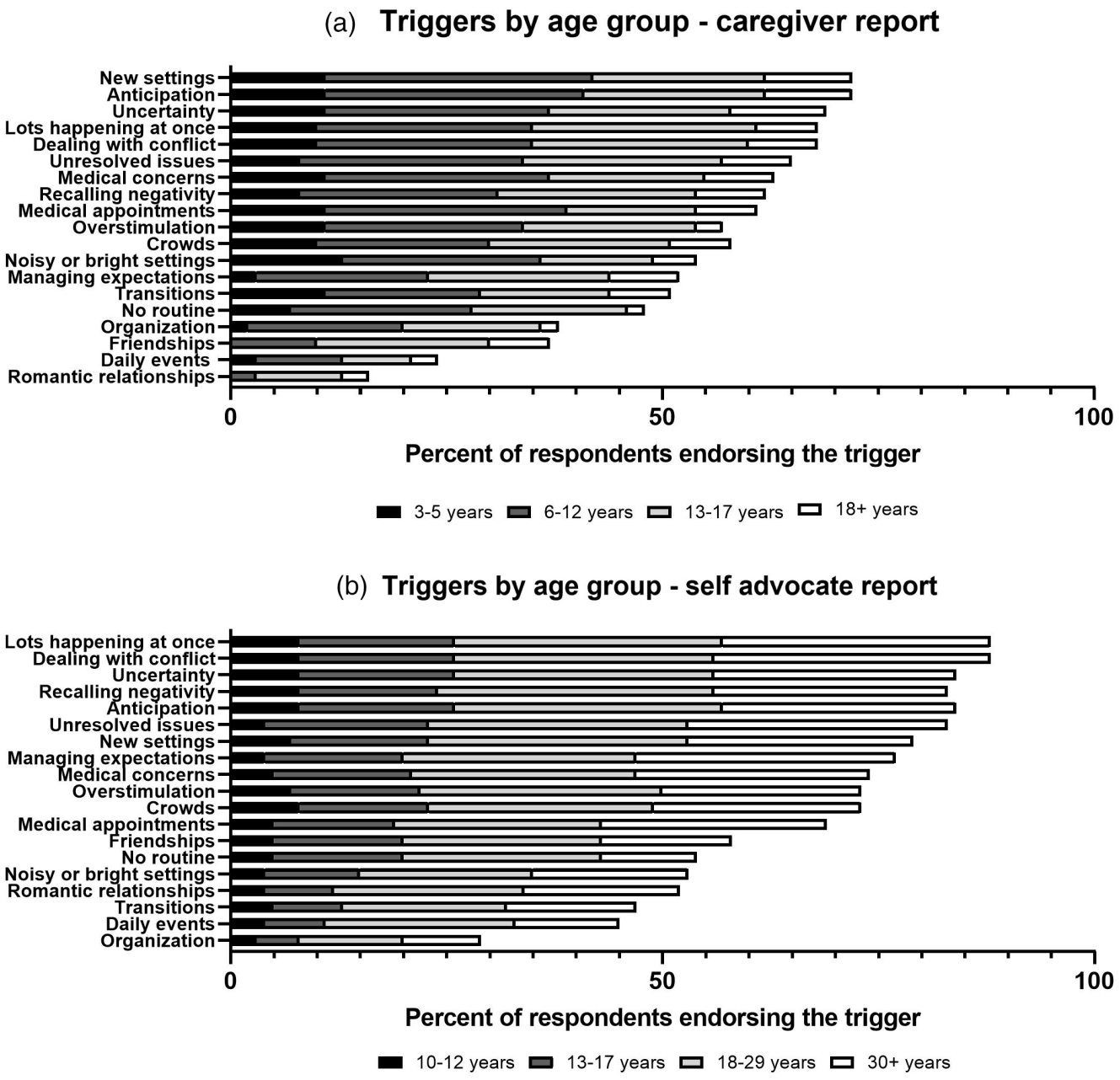

FIGURE 4 Reported triggers of anxiety endorsed (responded with likely or extremely likely) by each reporter group, broken down by age category. *$p < 0.05$.

over age 30 ($p = 0.001$)). Additionally, symptoms approaching significance for self-advocate age group differences included resistance and repetitive movement (both higher in adults 18–29 years, $p = 0.05$ and $p = 0.075$, respectively), fidgeting (lower in adults aged 30 or older, $p = 0.078$), and shakiness (lower in adolescents aged 13–17 years, $p = 0.058$).

3.2.2 | Triggers for anxiety

The top triggers for anxiety reported by caregivers were 'anticipation' and 'new settings' (77.2% each), 'uncertainty' (75.4%), 'lots happening at once' and 'dealing with conflict' (71.9% each). Similarly, the top triggers for anxiety reported by self-advocates were 'lots happening at once' and 'dealing with conflict' (92.9% each), followed by 'anticipation', 'uncertainty', and 'recalling negativity' (88.6% each).

Similar to symptoms, some triggers showed a linear relationship with age. Per caregiver report, the triggers of 'dealing with conflict' (OR: 1.09, 95%CI: 1.00–1.18, $p = 0.03$), 'managing expectations' (OR: 1.16, 95%CI: 1.07–1.28, $p = 0.002$), and 'recalling negative events' (OR: 1.08, 95%CI: 1.00–1.18, $p = 0.03$) increased with age. 'Managing expectations' increased with age (OR: 1.05, 95%CI: 1.01–1.10, $p = 0.01$) per self-advocate report as well.

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TABLE 2 Solutions for mitigating anxiety.

	Caregiver report			Self-advocate report		
	N, tried	%, tried	%, helpful	*N*, tried	%, tried	%, helpful
Bringing along a friend	44	78.6	86.4	61	84.7	91.8
Calming activity	53	94.6	84.9	68	93.2	92.6
Homeopathic	13	23.2	69.2	35	47.9	60.0
Journaling	23	41.1	56.5	55	76.4	72.7
'Mental health day'—taking an intentional day off	34	60.7	85.3	49	67.1	81.6
Moving around	50	89.3	64.0	65	90.3	78.5
Observing before joining	48	85.7	70.8	65	89.0	78.5
Prescribed medications—as needed (e.g., Xanax)	10	17.9	70.0	33	45.2	78.8
Prescribed medications—daily (e.g., SSRIs)	14	25.0	85.7	40	54.8	82.5
Reading about anxiety	26	46.4	38.5	38	52.1	52.6
Removing the expectation	44	78.6	77.3	62	84.9	74.2
Talking through anxiety	54	96.4	85.2	68	95.8	85.3
Therapy for anxiety	32	57.1	71.9	50	69.4	84.0
Visualization	34	60.7	67.6	51	71.8	52.9

Note: Percent helpful represents the proportion of those who had tried a strategy and reported it was 'sometimes', 'often', or 'almost always helpful'.

Triggers for anxiety were also analyzed by age groups; frequencies and *p*-values for age group differences are reported in Table B2 and represented visually in Figure 4. Significant group differences for triggers included caregiver report that 'organization' was more frequently a trigger for anxiety in school-age and adolescent children ($p = 0.037$) and that 'friendships' were more frequently reported triggers in adolescence and adulthood ($p < 0.001$). Self-advocate responses indicated 'unresolved issues' and 'managing expectations' were less often triggers for anxiety in pre-adolescent children ($p = 0.007$ and $p = 0.021$, respectively).

3.2.3 | Strategies to mitigate anxiety

Caregivers and self-advocates reported trying multiple strategies to mitigate anxiety, including evidence-based clinical treatments and lifestyle changes (Table 2). The strategies most often *tried*, reported by caregivers and self-advocates, were talking through the anxiety (96.4% and 95.8%, respectively), doing a calming activity (94.6% and 93.2%, respectively), moving around (89.3% and 90.3%, respectively), and observing an activity before joining (85.7% and 89.0%, respectively). Caregivers reported the most *helpful* strategies were bringing along a familiar friend (86.4%), taking daily anxiety medications (85.7%), taking a 'mental health day' (85.3%), and talking through the anxiety (85.2%). Self-advocates reported the most *helpful* strategies were doing a calming activity (92.6%), bringing along a familiar friend (91.8%), talking through the anxiety (85.3%), and ongoing therapy (84.0%). The total number of strategies used to mitigate anxiety increased with age per caregiver report ($p = 0.002$). Evidence-based treatments for anxiety were reported as helpful strategies for most respondents *who had tried them*, including therapy (caregivers = 57%, self-advocates = 84%), prescribed as-needed anxiety medication (e.g., Xanax, Klonopin, etc., >70%), and prescribed daily medications (e.g., SSRIs, etc., >80%).

Most respondents reported a history of receiving clinical anxiety treatment at some point in their life (Table 2). Of those who reported not having ever received treatment (21 caregivers, 27 self-advocates), the two most reported reasons were it was 'never offered' (24% caregivers, 31% self-advocates) and 'not interested in treatment at this time' (33% caregivers, 19% self-advocates).

3.3 | Qualitative results

Three broad overarching themes with 12 subthemes are supported by illustrative quotes in Table 3.

3.3.1 | Theme 1. Triggers are related to TS

Both self-advocates and caregivers conveyed multiple triggers for anxiety that related to having TS. Participants reported anxiety related to managing schoolwork, staying organized, and school performance—all congruent with the executive function and learning deficits associated with TS. Many participants reported anxiety with social situations that required understanding social cues and relating to peers, which led to anxiety surrounding making new friends and socializing in groups. Medical complications related to TS, including trauma from early surgeries and excessive fear of doctors' offices and needles, were reported by caregivers. Self-advocates described worries related to health outcomes, including fears about future heart failure, related to TS. Finally, interviewees reported general feelings of being different as causing them to feel anxious, including having a rare genetic

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TABLE 3 Themes, subthemes, and illustrative quotes.

Theme 1. Anxiety triggers are related to TS
Subtheme 1. Executive function and learning problems
"She definitely has anxiety about meeting deadlines and keeping track of everything and understanding expectations." Parent of teen with TS
"Because of Turner syndrome. I don't have great executive functioning skills…like organization, being able to like get things done, being productive at online school. There was just something about it that just triggered a part of my brain. It was just like I kind of just felt like I was drowning, and that I was constantly behind, and it just felt like a huge effort to get everything done. And then it just kind of, because I was feeling so much anxiety about that, it made anxiety in other parts of my life where I hadn't had that much anxiety also increase as well." Teen with TS
Subtheme 2. Social skill deficits
"[Anxiety] plays a role in her ability to engage socially. So, we are kind of always managing anxiety despite being able to still do life the way we want." Parent of child with TS
"In certain basic social situations that wouldn't cause anxiety for the average person, it might for me because of my Turner syndrome. Especially knowing that I'm not always the best with social situations. Like, I start having that anxiety right away." Adult with TS
Subtheme 3. Medical risks and procedures
"Blood draws and stuff are a big, huge deal. She's worried for weeks beforehand… she's very fearful and anxious of that kind of medical procedures." Parent of teen with TS
"Anxiety's definitely the hardest part of all of her medical issues that we've had to deal with… She has a surgery on Monday. Something now with her ear. So, for about 2 weeks now she's just been almost intolerable to deal with, fighting with her sisters about everything, upset about everything, unable to sleep at night, just because she knows the surgery is coming." Parent of teen with TS
"Sometimes the health anxiety or the thing I'm worried about has a little more validity to it just because of the fact that I have Turner syndrome and certain things being more likely or being associated with Turner Syndrome." Older teen with TS
"I don't want Turner syndrome to cause me anxiety because it's who I am, and I don't want to be scared of something like that … I don't want to be worried about like a heart surgery I'm gonna have to have in like 30 or 40 more years." Teen with TS
Subtheme 4. Being different
"She has anxiety around being different, and she often talks about how she's different because she has Turner syndrome. And so, I think that she feels having Turner syndrome also gives her anxiety." Parent of child with TS
"Sometimes telling people that I can't have kids and why I can't have kids can be anxiety inducing, because that's a little bit of a weird topic. But they asked me, and I don't want to lie." Adult with TS
Theme 2. Anxiety impacts the whole family
Subtheme 1. Mothers carry high burden for support
"We're walking such a tight line right now, like, we've got it. We've got it under control. I know how to handle it, and I'm scared to do anything else." Mother of teen with TS
"[My mom] was the one who was taking me to all my appointments, so then, she knew all the things… I think that definitely affected my mental health in that way, like building that sort of dependency." Older teen with TS
Subtheme 2. Separation anxiety
"She's very, very attached to me, and very protective of me almost to a bad point … She's very protective of me and does not like to be away from me." Mother of teen with TS
"I've always had separation anxiety … I don't like being apart from my mom." Older teen with TS
Subtheme 3. Accommodations may reinforce anxiety
"She's scared to death of the dark, and [her therapist] kind of told me everything I was doing like laying with her, turning on music, turning on lights, was probably reinforcing all that." Parent of teen with TS
"My mom was doing what any mom would try to do, she wanted me to feel better. So, she would kind of accommodate it, she would let me watch videos on her phone or on an iPad to distract myself, she would reassure me, she would do things for me, because I was avoiding them or anxiety had like, impaired my functioning too much." Older teen with TS
Subtheme 4. Poor sleep
"Night times were just a nightmare, lots of screaming and crying. It would get to the point where she would start pulling out her hair, scratching me, hitting me, just having a meltdown anytime we said it was time for bed. So, I would have to lay with her … [She] can't relax. Can't shut off her brain." Parent of teen with TS
"Fun Fact, I didn't sleep, for like the first 7 years of my life. I don't remember that. Supposedly it was horrible. I almost killed my mother. Like she was not having a great time." Teen with TS
Subtheme 5. Siblings
"It was a lot harder on [her siblings] when they were younger, because they didn't really understand … Now, they're actually kind of to the point where we know, I hate to say, but we all know when we have to walk on eggshells around her." Parent of teen with TS

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TABLE 3 (Continued)

Theme 3. Opportunities for early identification/intervention
Subtheme 1. Missed early signs of anxiety
"It was all more about height and heart and kidneys and thyroid … I don't think the sleep or any of that mental stuff is really mentioned much [by TS doctors]." Parent of a teen with TS
"I didn't know that [anxiety] could be an issue at the beginning. So, I know it was quite a while ago, so I don't know if [TS doctors] really knew that much about anxiety. … I didn't have any idea about the anxiety until we'd already kind of figured out that's what that was. Might have been nice if, looking back now, if I had that information." Parent of teen with TS
Subtheme 2. Lack of knowledge of association between anxiety and TS
"The behavior, especially when they are younger, we don't recognize as anxiety. We see meltdowns. That's what a lot of us call it. We see meltdowns, or trouble adjusting when things don't go right, or perfectionism." Parent of teen with TS
"In my experience, having, you know, like, co-occurring physical and mental health conditions, you kind of were getting one or the other. Like, your medical providers don't really get the mental aspect and your therapy team don't really get that physical health stuff." Teen with TS
Subtheme 3. Appreciation for early conversations about anxiety
"We started talking to her about it in kindergarten and we just sort of started explaining. So, we used a kids book about anxiety… That's when we started the play therapy. But we talked a lot about how we'd go to this person, you can go play with them, and they can help you understand anxiety or how you're feeling, and then help you learn how to manage it." Parent of child with TS
"I feel like my doctors always did a very good job of just making clear what would be up for me in the future. If that makes sense. I kind of knew, like, oh yeah, I'm gonna end up on anxiety medication because my anxiety is probably going to get worse at some point." Teen with TS

condition, looking different from family and peers, infertility, and interacting with the world differently.

3.3.2 | Theme 2. Anxiety impacts the whole family

Participants reported that anxiety had a strong impact on the entire family system. Self-advocates and caregivers recognized the role of mothers as the family member who carried most of the burden of their daughters' anxiety. Adolescent and young adult self-advocate interviews revealed self-awareness of a persistent dependence on mothers, including acknowledgment of separation anxiety well past childhood. Although mothers shouldered the primary burden, caregivers also reported that siblings had to cope with anxiety in the home, including knowing when to leave their sibling with TS alone, sleeping in the same room to provide comfort, or helping them make friends. Caregivers described trying a myriad of strategies to manage their child's anxiety, including complex mental health care plans, calming strategies in the home to prevent or reduce anxiety symptoms, and removing known triggers from their daughters' daily lives. Both self-advocates and caregivers reported that these accommodations did not build self-coping skills and sometimes exacerbated anxiety symptoms. Sleep disturbance was a persistent symptom that impacted the whole family. Interviewees reported a variety of sleep-related concerns, including problems falling asleep, staying asleep, and daytime fatigue. Elaborate bedtime routines and co-sleeping were reported well into adolescence.

3.3.3 | Theme 3. Opportunities for early identification/intervention

Across participants, there was a clear sense that anxiety in TS can and should be identified and managed early in life. Many caregivers and self-advocates reported that they did not learn about anxiety as a potential concern with the initial diagnosis of TS. Early signs of anxiety (e.g., meltdowns, perfectionism, anger, and hyperactivity) were often misinterpreted as behavior problems. For interviewees who did have early conversations about anxiety with healthcare providers, both caregivers and self-advocates expressed appreciation and reported these early conversations helped them understand these symptoms as anxiety.

3.4 | Mixed methods results

Table 4 shows how qualitative findings were consistent with, expanded upon, or diverged from quantitative results.

4 | DISCUSSION

The current study is the first to describe anxiety symptomology and care experiences for individuals with TS using a community-engaged, mixed methods approach. These findings provide unique insight as to how and why individuals with TS experience anxiety and the facilitators and barriers to their care. These data are critical to addressing the underdiagnosis of anxiety in youth with TS and identifying effective anxiety screening, diagnosis, and treatment options to improve quality of life for patients with this complex and rare genetic condition.

Many behavioral and physical manifestations of anxiety for people with TS align with symptoms described by DSM criteria for anxiety disorders common in the general population (generalized anxiety disorder, social phobia, and separation anxiety disorder; American Psychiatric Association, 2015). Frequently endorsed symptoms included both internal anxiety experiences caused by an activated sympathetic nervous system (e.g., body tension, increased heart rate, and digestive

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TABLE 4 Joint display triangulating statistical results with qualitative findings.

Quantitative	Qualitative themes and subthemes	Mixed-methods inferences
>70% of all respondents endorsed insomnia as a symptom of anxiety	Theme: Anxiety impacts the entire family Subtheme: Sleep problems	*Expansion*: Interview data expanded upon survey results showing that insomnia was the most frequently endorsed symptom of anxiety. Anxiety-related sleep problems impacted the entire family system, requiring excessive supports from parents and siblings well into adolescence.
Per self-advocate report, clinging decreased with age (OR: 0.96, 95%CI: 0.92–0.99, $p = 0.02$). Within the adolescent sub-group, 79% of caregivers, 73% of self-advocates endorsed clinging as a sign of anxiety.	Theme: Anxiety impacts the entire family Subthemes: Separation anxiety; Accommodations may reinforce anxiety	*Expansion*: Clinging to a parent or trusted adult was endorsed as a symptom of anxiety in all age groups, and although it decreased with age, clinging was still commonly endorsed in the adolescent age group. Interview data expanded upon this finding revealing that early experiences of mothers managing frequent TS-related medical procedures and accommodating frequent anxiety in the household sometimes led to clinginess and a lack of independence.
Frequently reported triggers for anxiety included 'managing expectations,' 'dealing with conflict,' and 'medical concerns'	Theme: Anxiety triggers are related to TS Subthemes: Executive function and learning problems; Social skill deficits; Medical risks and procedures; Being different	*Expansion*: Surveys results and interviews expanded upon each other, as respondents endorsed triggers for anxiety that are related to features common in the TS phenotype including executive functioning problems, social cognition deficits, and medical concerns. Emergent findings not accounted for in the survey, included that a sense of non-belonging related to having a rare disease like TS contributed to anxiety.
Anxiety treatments increase with age ($p = 0.002$).	Theme: Opportunities for early identification/intervention Subtheme: Missed early signs of anxiety	*Confirmation*: Survey results showing younger participants had received fewer anxiety treatments were confirmed in interviews. Participants described milder, but still noticeable, symptoms of anxiety in early childhood were often missed and not treated until later in life when symptoms were more severe.
~One-third of participants (34% caregivers, 36% self-advocates) had never received treatments for anxiety. The most frequently reported reason was that treatment was 'never offered' (24% caregivers, 31% self-advocates).	Theme: Opportunities for early identification and intervention Subtheme: Lack of knowledge of association between anxiety and TS	*Confirmation*: Qualitative data confirmed that many patients with TS are not offered treatment for anxiety by their medical team. Interviews elucidated a general lack of awareness that anxiety may be associated with the TS phenotype and a clear priority to treat TS-related medical features over mental health concerns.

problems) and observable behaviors (e.g., anxious facial expressions, avoidance, clinging, and repetitive speech). Sleep disturbance is highly prevalent in children with anxiety disorders (Brown et al., 2018), and insomnia was consistently among the top symptoms experienced in our study across all age and rater groups. Individuals with TS are also at a great risk for sleep disordered breathing and sleep apnea (Gravholt et al., 2017; Pham et al., 2023), which may contribute to poor sleep health in addition to or in the absence of anxiety. There is remarkably little in the literature about sleep health in TS, but insomnia could be an early observable sign that an individual with TS is experiencing anxiety, as there is a reciprocal relationship between sleep disturbance and anxiety in the general pediatric population (Brown et al., 2018). Future research should address sleep health in individuals with TS, including subjective sleep experiences and relationships between insomnia, anxiety diagnoses, and other sleep diagnoses.

Both symptomatology and triggers for anxiety changed across the lifespan (i.e., decreasing aggression, tantrums, and clinging, and increasingly triggered by conflict, managing expectations, and recalling negative events), but these changes were not always linear with age (i.e., organization as a trigger mostly for school-age children and friendships as a trigger mostly for adolescents). As anxiety can manifest in a variety of ways and may be triggered by new events at different life stages, symptoms may go unrecognized by caregivers, educators, or medical providers. This was supported by our qualitative findings, in which participants described missing early signs of anxiety (e.g., perfectionism, tantrums, and aggression) and opportunities to intervene before more severe symptoms with a greater impact on daily functioning were present. Figures 3 and 4 may be useful tools to educate clinicians and families about what to look for when monitoring for anxiety in TS across the lifespan.

Many participants' anxiety triggers were directly related to the lived experience of having TS. Individuals with TS are at increased risk for executive functioning deficits (Green et al., 2015), reduced social cognition (Jordan et al., 2023; Wolstencroft & Skuse, 2019), cardiovascular disease (Kozlowska-Wojciechowska et al., 2006), dysmorphic features (Kruszka et al., 2020), and infertility (Hewitt et al., 2013), all of which were endorsed in the survey or identified through interviews as triggers for anxiety. Our results indicate that anxiety might be triggered more frequently in school settings where executive function

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and social demands increase. Accordingly, teachers and school support teams should be integral members of the care team and should be provided with resources on the unique learning profiles and medical risks associated with TS. Classroom accommodation and school-based mental health supports for anxiety should also be considered when developing educational programs for students with TS.

Participants expressed that simply having TS caused them to feel different from their peers and family and led to apprehensive expectations and fears about health complications for which they were at increased risk. While there is no literature specific to TS, providers should assess for medical anxiety in patients with TS and consider child-life and/or psychological support to help address this if present. Overall, our findings support that multidisciplinary TS care teams should include neuropsychology, clinical psychology, and social work to assess learning needs, diagnose mental health conditions, and link families to mental health providers in their community.

Our results were promising in that participants reported multiple evidence-based interventions and lifestyle strategies as helpful tools to mitigate symptoms of anxiety. Consistent with the literature on anxiety treatment in the general population, most survey respondents who had tried therapy and/or medication reported these strategies were somewhat to mostly helpful in reducing anxiety. Research has shown selective serotonin reuptake inhibitors (SSRIs) are safe and highly efficacious in children and adolescents with anxiety in the general population (Strawn et al., 2018; Walter et al., 2020), and thus should be considered as an important component of treatment for individuals with TS presenting with anxiety symptoms. Cognitive behavioral therapy (CBT) and exposure-based therapy are well established therapeutic modalities for anxiety, with robust evidence in both general pediatric populations as well as other populations of children with neurodevelopmental disorders (Freidl et al., 2017; Wood et al., 2020). Our respondents showed positive response to these evidence-based interventions; data which support the idea of future clinical trials to evaluate specific therapy modalities and medications to address anxiety in TS.

However, despite reported positive experiences with these treatments and other anxiety–mitigation strategies, participants still reported high levels of anxiety. It is possible that while many evidence-based strategies successfully reduce anxiety symptoms in the short term, the lifelong and pervasive health problems associated with TS demand TS-specific treatment options across the lifespan. As we heard in the qualitative phase of the study, families report myriad interventions are needed to aid with many different manifestations of anxiety. Our quantitative results also showed that as individuals age, new symptoms or triggers arise, which then require new strategies; there is not one simple solution for families impacted by TS. Future clinical trials should build upon these findings, employing both interventions and outcome measures adapted for TS.

For example, respondents frequently endorsed that talking through their anxiety was a useful strategy, and the documented TS phenotype includes relative strengths in verbal reasoning and communication (Hong et al., 2009). This suggests talk therapy strategies such as CBT may be feasible and acceptable for many individuals with TS. Thematic findings that anxiety in TS impacts the entire family system also support the idea of family-based mental health interventions to provide support for parents and encourage healthy family responses to anxious behaviors. These findings suggest a need for active parent coaching as a component of anxiety intervention, as caregiver accommodation of anxiety is often a major factor for maintenance of mitigation strategies. Family-based therapeutic interventions have been shown to be helpful for adolescents, including other clinical populations (Reaven et al., 2012; Sigurvinsdóttir et al., 2020), but will likely need tailoring to meet specific needs related to TS identified in this study, such as frequent invasive medical procedures, executive function and learning challenges, social skill deficits, and looking and feeling different from peers due to the genetic difference.

4.1 | Limitations

Despite our relatively large sample size for research in a rare genetic condition and our responsiveness to community priorities through CPBR, this study had several limitations. Our CAB had three self-advocate members; however, only one was able to attend the final two CAB meetings, which may have limited our community-based interpretation of qualitative findings. Future CAB work should require at least two patient advocates at each CAB meeting to ensure diversity of opinions and to limit CAB member discomfort with a need to represent all individuals with TS. Additionally, representation from a psychiatrist who sees adult patients will be important in future research focusing on anxiety in adult Turner syndrome patients.

Pragmatic limitations included the sequential design of the study. While best practice in qualitative research recommends continuing data collection until thematic saturation is achieved (Morse, 1995), funding and timing allowed for only 10 interviews (five per stakeholder group). Further, CAB priorities and quantitative results led us to purposely sample across a range of ages. As a result, we continued to hear new themes throughout the interviews. Although we feel we had adequate 'information power' (Malterud et al., 2016) to report on the three themes presented here, themes may have been more complex or additional themes may have emerged from the data if we had persisted with qualitative data collection. The study design also limited our ability to verify reported comorbid psychological diagnoses. As such, we were unable to adequately analyze anxiety symptoms, triggers, or solutions in the context of comorbid ADHD, learning disorders, or ASD which were all emergent themes identified as triggers in the qualitative interviews. Future work should include confirmed comorbid psychosocial diagnoses or symptoms as covariates in any analysis of anxiety in TS.

While participants had the opportunity to participate as a dyad (i.e., both parent and child completing the respective surveys), it was not required, and we did not have enough participants to conduct paired analysis. Future research should purposely sample dyads so that potential parent/child differences can be identified. We did not adjust for multiple comparisons as cell sizes were relatively small and this study was meant to be exploratory and hypothesis generating

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(Feise, 2002). Notably both specific phobias, other than agoraphobia, and separation anxiety were not specifically asked as comorbid diagnoses. As themes related to separation and phobias did emerge in the qualitative findings, our future work will more specifically investigate these diagnoses. Finally, this study is limited by a homogeneous sample in terms of race, ethnicity, and socio-economic status. Most participants identified as White, non-Hispanic, with higher educational attainment and income than the general US population. Research in rare disease is often limited by overrepresentation from majority demographic groups (Halley et al., 2023) and despite efforts to recruit a more diverse sample (e.g., survey in multiple languages, recruitment in diverse clinic setting, and use of highly diverse registry), our study perpetuates this trend. As mental health is tied to social determinants of health, future research should intentionally partner with underrepresented communities within the TS patient population to improve our understanding of the complicated relationship between TS and anxiety across cultures and backgrounds.

4.2 | Future directions and conclusions

This community-based participatory study found that while many symptoms of anxiety in individuals with TS overlap with DSM criteria for anxiety disorders, there are some unique patterns for anxiety triggers directly related to the TS phenotype which may make this patient population particularly vulnerable. Future directions of this work include improving anxiety screening procedures to capture these unique features and testing the effectiveness of anxiety-specific behavioral health and medication interventions to improve overall quality of life in TS. The findings of this analysis can be used to guide future research on anxiety in TS and inform clinical care recommendations regarding anxiety screening, diagnosis, and treatment practices.

AUTHOR CONTRIBUTIONS

Alexandra Carl: formal analysis, data curation, methodology, project administration, and writing—original draft/review and editing. **Marybel Good**: conceptualization, funding acquisition, formal analysis, project administration, and writing—original draft/review and editing. **Erica Haag**: formal analysis and writing—review and editing. **Christa Hutaff-Lee**: project consultation and writing—review and editing. **Deanna Swain**: project consultation and writing—review and editing. **Nicole Tartaglia**: project consultation and writing—review and editing. **Casey Sakamoto**: methodology, statistical analysis, software, writing—review and editing. **Shanlee Davis**: conceptualization, methodology formal analysis, funding acquisition, and writing—review and editing. **Talia Thompson**: conceptualization, data curation, methodology formal analysis, funding acquisition, project administration, and writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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