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# Characterizing the Anxiety Phenotype in Triple X Syndrome

Rebecca Wilson, PsyD<sup>1,2</sup>, Kristen Withers Wigby, MD<sup>3</sup> and Nicole Tartaglia, MS, MD<sup>1,2</sup>

1. University of Colorado School of Medicine, Developmental Pediatrics
2. eXtraordinary Kids Clinic, Children's Hospital Colorado, Aurora, Colorado
3. University of California – San Diego, Dept. of Genetics, San Diego, California



## BACKGROUND

- Triple X syndrome occurs in approximately 1 in 1000 female births.
- It can be associated with developmental delays and psychological differences.
- The behavioral phenotype of Triple X includes anxiety and shyness.
- In a 2014 study by Lenroot et al. that included 35 participants with Triple X syndrome (age 5-24 yo), 83% reported symptoms of anxiety and 40% met DSM-IV criteria for an anxiety disorder using K-SADS standardized interview. (Ref: [PMC4241137](#))

## STUDY AIMS

- In this project we aimed to characterize the anxiety phenotype associated with Triple X syndrome by evaluating profiles of anxiety-related behaviors and symptoms at different stages of development.

## METHODS

- Females with nonmosaic Triple X were recruited for an ongoing IRB-approved study on health and development in sex chromosome disorders.
- Participants included 74 individuals with Triple X who responded to research recruitment and those seeking clinical evaluation and treatment in a specialty clinic for sex chromosome aneuploidy.
- 9 participants <3 years of age or >25 years of age were excluded, leaving 65 participants.
- The subgroup with anxiety were identified by evaluating results of a parent-reported behavioral symptom checklist, a standardized behavioral questionnaire (BASC-2), and previous medical / psychological records.
- This Anxiety subgroup (n=51) was divided into 3 age groups (2-6y, 7-11y, and 12-24y)
- Results of the behavioral symptom checklist were analyzed to compare frequency of behavioral symptoms between age groups
- A subset of participants received a **team clinical evaluation** (n=30), including psychological evaluation. These medical records were reviewed and clinical findings summarized.

**Total Triple X group Age 2-24: N=65**

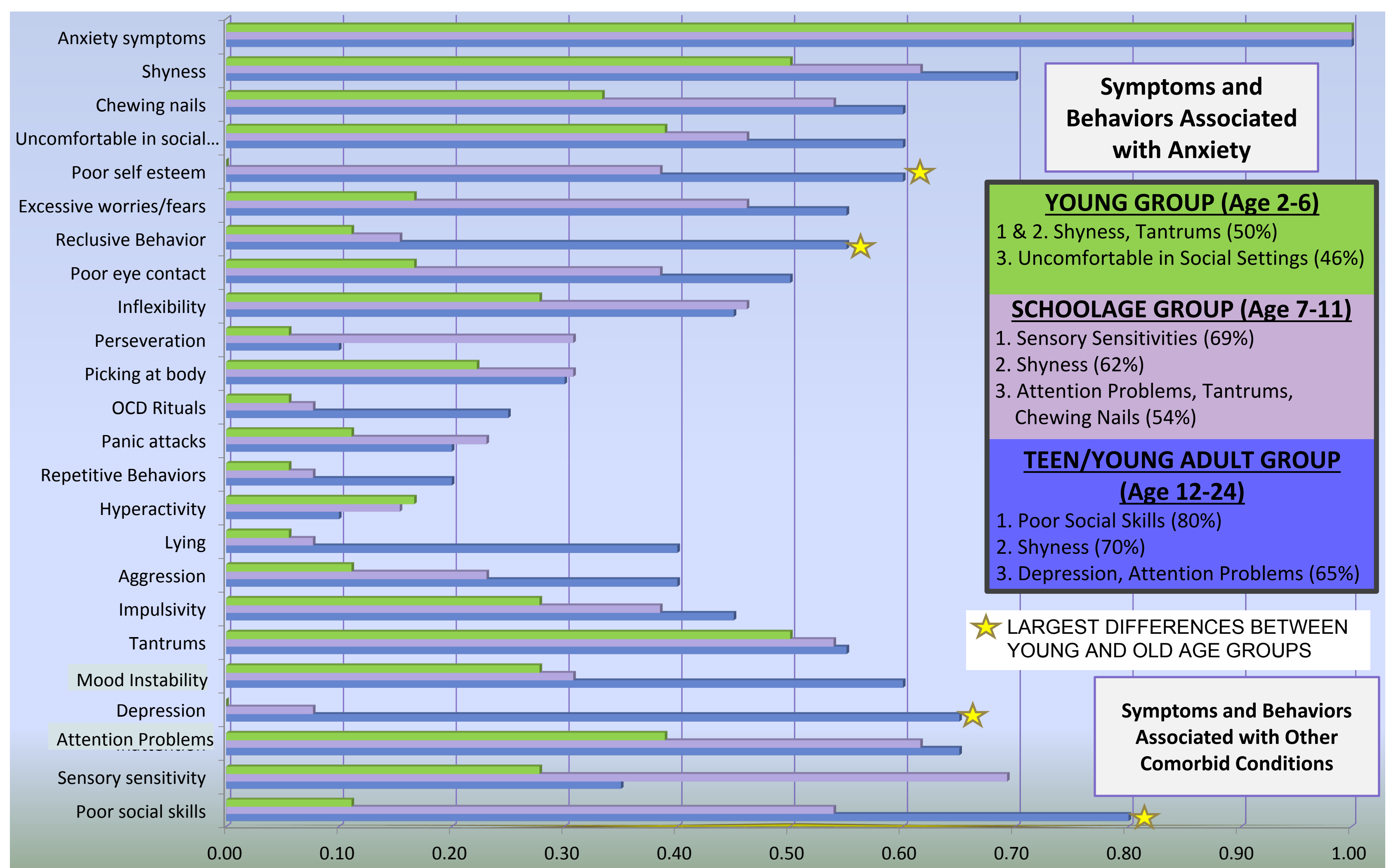
Age: Mean =10.32, Median 9.75, Range=2.25 to 24.58

Behavioral Symptom Checklist Positive for Anxiety or  
BASC-2 Anxiety T score >60 or  
Previous clinical diagnosis of anxiety disorder

**Anxiety Group: N=51/65 (78.4%)**

YOUNG ANXIETY GROUP Age 2-6 years n=18/26 69.2%	SCHOOLAGE ANXIETY GROUP Age 7-11 years n= 13/15 86.6%	TEEN/YOUNG ADULT ANXIETY GROUP Age 12-24 years n= 20/24 83.3%
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## RESULTS: Behavioral Symptoms in Anxiety Group (n=51)



**Symptoms and Behaviors Associated with Anxiety**

**YOUNG GROUP (Age 2-6)**  
1 & 2. Shyness, Tantrums (50%)  
3. Uncomfortable in Social Settings (46%)

**SCHOOLAGE GROUP (Age 7-11)**  
1. Sensory Sensitivities (69%)  
2. Shyness (62%)  
3. Attention Problems, Tantrums, Chewing Nails (54%)

**TEEN/YOUNG ADULT GROUP (Age 12-24)**  
1. Poor Social Skills (80%)  
2. Shyness (70%)  
3. Depression, Attention Problems (65%)

★ LARGEST DIFFERENCES BETWEEN YOUNG AND OLD AGE GROUPS

**Symptoms and Behaviors Associated with Other Comorbid Conditions**

## SUMMARY OF BEHAVIORAL SYMPTOMS IN ANXIETY GROUP BY AGE GROUP

- Rates of most behaviors increased in the older age groups
- Immature emotional regulation appears elevated in older age groups
- Externalizing behaviors are more elevated than might be expected
- The largest age group differences were found in: (p<0.05 on Fisher's Exact)
  - Low Self-esteem
  - Depressive symptoms
  - Poor social skills
  - Reclusive behavior

## RESULTS: Team Clinical Evaluation (n=30)

N=30	Anxiety Disorder Diagnoses	Other Diagnoses	% Prenatal Diagnosis	Verbal IQ	Non-verbal IQ	Full Scale IQ	Adaptive Functioning Composite
Age 3-5 N=12	• Generalized Anxiety Disorder 2/12 • Selective Mutism 3/12*	• ADHD 2/12 • Sensory Disorder 3/12 • Speech Disorder 3/12	75%	103.7 ± 14.3	107.9 ± 5.8	108.1 ± 9.5	94.11 ± 18.15
Age 7-11 N=7	• Generalized Anxiety Disorder 2/7 • Social Anxiety Disorder 1/7 • Separation Anxiety Disorder 1/7	• ADHD 4/7 • Learning Disability 2/7 • Intellectual Disability 1/7	57%	81.29 ± 11.9	86.43 ± 12.2	82.86 ± 12.6	79.8 ± 8.9
Age 12-24 N=11	• Generalized Anxiety Disorder 7/11 • Specific Phobia 1/11	• ADHD 4/11 • Learning Disability 2/11 • Intellectual Disability 1/11 • Bipolar Disorder 1/11 • Dysthymia/Depression 3/11	45%	88.3 ± 9.2	90.2 ± 19.9	88.0 ± 14.9	70.14 ± 10.8

## RESULTS: Team Clinical Evaluation (n=30)

	No Anxiety Disorder N=15	Anxiety Disorder N=15	p
Age (yrs)	9.1 ± 5.7	11.2 ± 6.0	0.33
Prenatal Diagnosis	5/15	7/15	0.47
Verbal IQ <sup>1</sup>	89.9 ± 14.5	91.5 ± 15.9	0.79
Performance IQ <sup>1</sup>	92.0 ± 17.9	96.2 ± 17.8	0.58
Full Scale IQ <sup>1</sup>	93.4 ± 17.0	95.9 ± 17.4	0.70
Adaptive Composite <sup>2</sup>	86.5 ± 21.4	76.3 ± 10.7	0.09
BASC2 Anxiety T-score <sup>3</sup>	59.0 ± 14.4	57.6 ± 10.0	0.81
BASC2 Withdrawal T-score <sup>3</sup>	62.4 ± 17.2	71.8 ± 8.1	0.07
BASC2 Internalizing Composite T-score <sup>3</sup>	63.7 ± 12.5	63.3 ± 15.1	0.95
BASC2 Behavioral Symptoms Index T-score <sup>3</sup>	63.4 ± 11.6	66.4 ± 15.0	0.62

## CONCLUSIONS

- Anxiety symptoms and anxiety-related behaviors were very common in Triple X syndrome across age groups in this cross-sectional sample.
- Within the subset who received clinical evaluation, multiple different anxiety disorders were confirmed, along with other comorbid cognitive/learning, attentional and psychological diagnoses known to be associated with Triple X.
- Selective mutism was identified in 3 young girls of the 30 (10%) who received a clinical evaluation, a diagnosis previously unreported in Triple X syndrome.
- There were no differences in VIQ, PIQ, or FSIQ scores when comparing those with and without an anxiety disorder, however there was a trend toward lower adaptive scores when an anxiety disorder was present.
- Clinically significant anxiety disorders were present in at similar rates in girls with both a prenatal and postnatal Triple X diagnosis.
- There were no differences in the BASC-2 Anxiety Scale between those with and without clinical anxiety disorders, and the mean overall score was not elevated in either group. Further, the BASC-2 Withdrawal scale was higher in the group with confirmed anxiety disorder, and may be a better scale for identifying anxiety symptoms in Triple X. This finding may relate to less verbal expression of anxiety and more of a behavioral profile of anxious reactions.
- Some behaviors typically assumed to diminish with age increased in this cross-sectional study, most notably tantrums, aggression, poor eye contact and lying among other concerns that were more prominent in the older age group.
- Further research is needed to evaluate:
  - the interplay between anxiety and other features including cognitive and language deficits
  - prospective evolution of anxiety symptoms in a longitudinal cohort
  - the role of family mental health history and SES on anxiety symptoms
  - medical and psychological interventions

1. Evaluated by WASI, WISC-IV or WAIS-III  
2. Evaluated by Vineland-2 or ABAS-II  
3. BASC-2 = Behavioral Assessment System for Children – 2<sup>nd</sup> Edition