**Title**: Initial characterization of behavior challenges and relationship to quality of life in individuals with *ASXL*-Related Disorders

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**Introduction**: *ASXL*-Related Disorders (*ASXL*-RD) are rare neurodevelopmental disorders caused by pathogenic variants in the *ASXL1*, *ASXL2* or *ASXL3* genes and are characterized by feeding difficulties, multi-organ system dysfunction and intellectual disability (ID). Although severe behavior has been noted by caregivers as top priority for treatment, no study has systematically studied behavioral challenges in this population. The objective of this study is to describe scores on the Aberrant Behavior Checklist, Second Edition (ABC-2) and examine whether behavioral challenges are associated with lower quality of life (QoL) in a sample of individuals with *ASXL*-RD.

**Method**: Caregivers of 21 individuals with *ASXL*-RD (n *ASXL1*=4, n *ASXL2*=3, n *ASXL3*=14) between the ages of 1 and 26 years (M=10.5, SD=6.9) who attended the *ASXL* Rare Research Endowment Foundation Family Conference in Baltimore, Maryland in July 2024 participated. Caregivers completed the ABC-2 Community form, a 58-item questionnaire that asks caregivers to rate problem behaviors over the last month across five subscales including Irritability (15 items), Social Withdrawal (16 items), Stereotypic Behavior (7 items), Hyperactivity/Noncompliance (16 items), and Inappropriate Speech (4 items). Items are scored as 0 (not at all a problem), 1 (slight problem), 2 (moderately serious problem), or 3 (severe problem). Higher subscale scores suggest greater challenging behavior. Caregivers also completed the Quality of Life Inventory-Disability (QI-D), a 32-item questionnaire that asks parents to rate behaviors reflecting their child’s QoL over the past month in the areas of Health and Well-being, Positive Emotions, Negative Emotions, Social Interaction, Recreational Activities and the Outdoors, and Independence. Higher QI-D Total scores suggest higher QoL.

**Results**: On the ABC-2, mean scores were as follows: Irritability=14.8 (SD=13.8), Social Withdrawal=11.1 (SD=10.9), Stereotypic Behavior=7.7 (SD=7.0), Hyperactivity & Noncompliance=17.0 (SD=15.5), Inappropriate Speech=2.5 (SD=4.3). Forty-three percent (n=9) had an Irritability score above 18, which is noted in the literature to indicate clinically significant behavior problems. Compared to the ABC-2 validation sample of children and adolescents with Intellectual Disability (ID), those with *ASXL*-RD demonstrated significantly higher scores on Irritability (t(607)=3.82, p<.001; ID M=7.83, SD=7.90), Social Withdrawal (t(607)=2.99, p=.003; ID M=6.16, SD=7.29), Stereotypic Behavior (t(607)=6.24, p=<.001; ID M=2.38, SD=3.66), and Hyperactivity and Noncompliance (t(607)=2.39, p=.017; ID M=11.20, SD=10.74), but not on Inappropriate Speech (t(607)=.85, p=.394; ID M=1.97, SD=2.62). On the QI-D, the mean Total score was 67.6 (SD=12.0). Higher ABC-2 Social Withdrawal scores were associated with lower QI-D Total scores (r=-.639, p=.002); however, no other significant correlations emerged between the ABC-2 subscales and the QI-D Total (all p>.05).

**Discussion:** Consistent with previous parent-report of severe behavioral challenges in *ASXL*-RD, findings indicate significant behavioral difficulties across nearly all areas assessed by the ABC-2. Additionally, greater behavioral challenges were related to lower QoL. Ongoing research in a larger sample is needed to better characterize these behavioral challenges by genotype to inform treatment and clinical trial readiness. Additionally, further work to better understand the relationship between these behavioral challenges and QoL is critical for improving the lives of children with these complex and rare disorders.