American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

RESEARCH LETTER OPEN ACCESS

Gene-Specific Growth Charts for *ASXL3*-Related Disorder

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Received: 7 November 2025 | **Revised:** 25 November 2025 | **Accepted:** 28 November 2025

Keywords: ASXL3 | charts | growth | LMSz

ASXL3-related disorder is a rare neurodevelopmental disorder first described by Bainbridge et al. 2013. It is caused by pathogenic variants in the *ASXL3* gene located on chromosome 18q12.1. Common features of the disorder include global developmental delay/intellectual disability, hypotonia, behavioral issues, and craniofacial features (Woods et al. 2024). Postnatal growth restriction and feeding difficulties are frequently observed, often necessitating clinical investigation and, in some cases, medical intervention. Consequently, ensuring access to growth monitoring equivalent to that available for the general pediatric population is essential. Early identification of deviations from *ASXL3*-specific growth trajectories may carry important clinical value by distinguishing expected postnatal growth patterns from those suggestive of additional underlying pathology.

Low et al. (2025) recently reported gene-specific growth charts for rare disease cohorts, including individuals with *ASXL3*-related disorder, using a novel statistical approach termed the LMSz method—an adaptation of the traditional LMS method (Cole and Green 1992) applied on the z-score scale. This methodology enables the development of clinically relevant growth charts derived from small cohort datasets, addressing a key limitation of conventional growth charts which require large numbers of measurements.

The *ASXL3*-specific growth charts presented in Low et al. (2025) were generated using 119 individual data points from participants enrolled in the UK Deciphering Developmental Disorders (DDD) study (Firth and Wright 2011) and the *ASXL3* International Natural History Study (Woods et al. 2025). All included individuals had pathogenic or likely pathogenic *ASXL3* variants, as per expert variant review and as per the relevant international ACMG standards (Richards et al. 2015; Riggs et al. 2020). Of these data points, 49 corresponded to females and 70 to males. The *ASXL3* International Natural History Study included participants from 13 countries across Europe, Australia, Canada, the United States, and Brazil, with the majority originating from the United Kingdom (Woods et al. 2025).

We subsequently applied the LMSz methodology to an expanded *ASXL3* dataset comprising 136 data points from 98 unique individuals less than 18 years of age. Of these, 56 data points corresponded to females and 78 to males. The dataset included 212 measurements for weight (113 excluding birth weight), 115 for height, and 76 for head circumference. Additional data were collected approximately one year after enrollment in the *ASXL3* International Natural History Study, supplemented with measurements reported in the medical literature (Srivastava et al. 2016; Schirwani et al. 2021, 2023).

No significant abnormalities in birth measurements were identified in the largest cohort study to date (Woods et al. 2025). However, postnatal growth abnormalities, including growth failure and microcephaly, are commonly reported features of the condition (Schirwani et al. 2021). Longitudinal natural history data indicate that although individuals generally continue to gain height and weight throughout childhood, postnatal growth is frequently suboptimal, with approximately half of affected individuals recording measurements below the 10th centile for two or more measures (Woods et al. 2025).

Using the LMSz method, sex-specific growth centiles were generated by back-transforming z-score centiles (Figures 1 and 2).

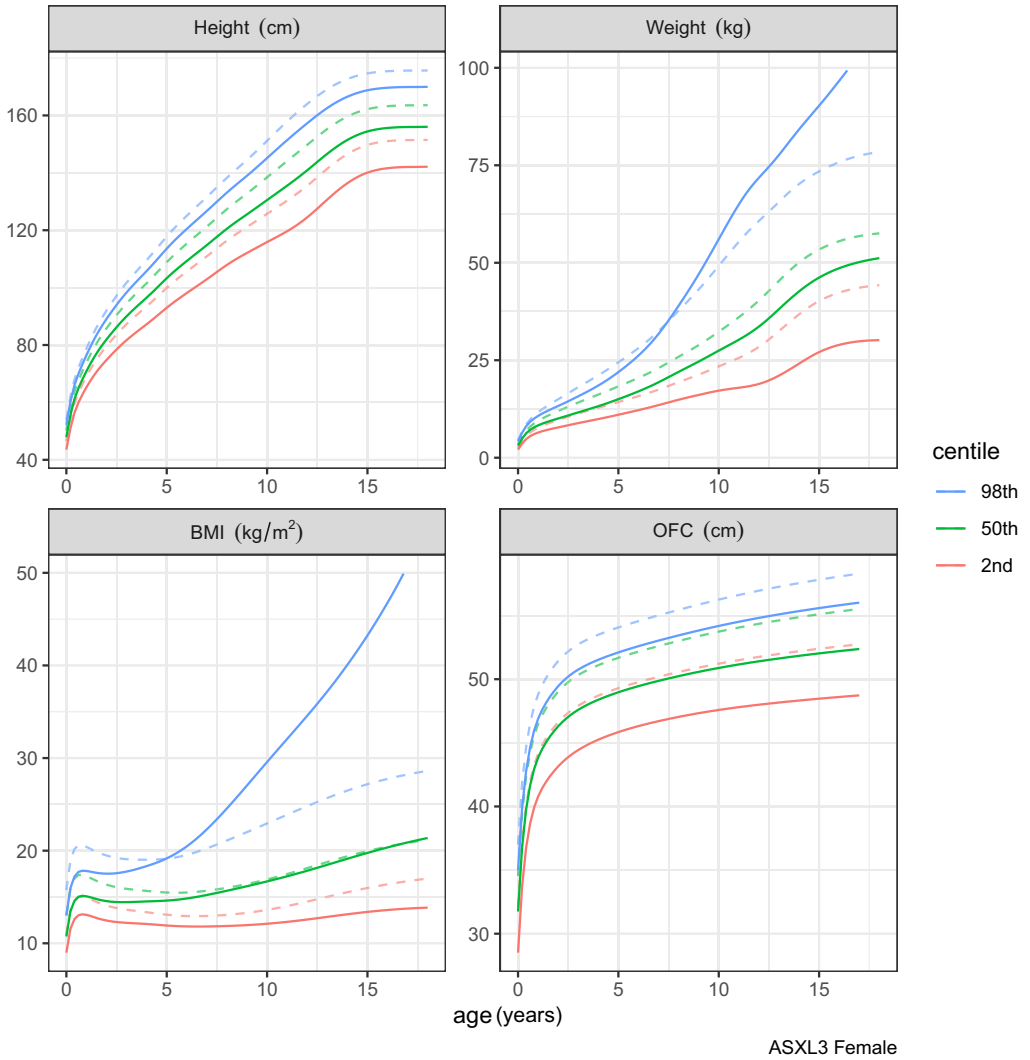

FIGURE 1 | *ASXL3*-specific measurement centiles for females. Corresponding British 1990 (UK90) centiles are shown as dashed curves.

The resulting growth charts demonstrate a downward shift in the 2nd, 50th, and 98th centiles for both height and head circumference (OFC) in males and females, consistent with the known postnatal growth restriction and proportionate postnatal microcephaly associated with the *ASXL3*-related disorder.

The growth charts also demonstrate a downward shift in the 2nd, 50th, and 98th centiles for weight and BMI during early childhood. Over one-third of individuals reported by Woods et al. (2025) were diagnosed with failure to thrive, most commonly during infancy, although in some cases this occurred later in childhood. Behavioral factors and medication side effects may somewhat contribute. For example, in the *ASXL3* Natural History Study, 14% of children received a diagnosis of attention-deficit hyperactivity disorder (ADHD), and a subset were treated with stimulant medications, which may further contribute to appetite suppression. However, the progressive widening between the 2nd and 98th centiles throughout childhood reflects substantial inter-individual variability and highlights the complex, multifactorial factors influencing growth in *ASXL3*-related disorder.

The growth charts also show an upward shift in the 98th centile for weight and BMI later in childhood. A small subset of individuals with *ASXL3*-related disorder exhibits a marked increase in BMI during this period, possibly reflecting a combination of altered appetite regulation, medication effects, and reduced physical activity. However, this pattern may not be specific to *ASXL3*-related disorder and could reflect broader population trends toward increasing obesity in adolescence, as observed in *KBG* syndrome-specific growth charts (Low et al. 2025). Consistent with recommendations for the general population, a healthy lifestyle—including balanced nutrition and regular physical activity—should be encouraged, with consideration of the individuals' potential additional needs.

Many individuals with *ASXL3*-related disorder experience feeding difficulties during childhood, sometimes resulting in the use of feeding adjuncts, such as nasogastric or percutaneous gastrostomy tubes, for varying durations. Growth of children is typically monitored using population growth charts, which may not accurately reflect the expected growth trajectory for children with a particular condition. This document

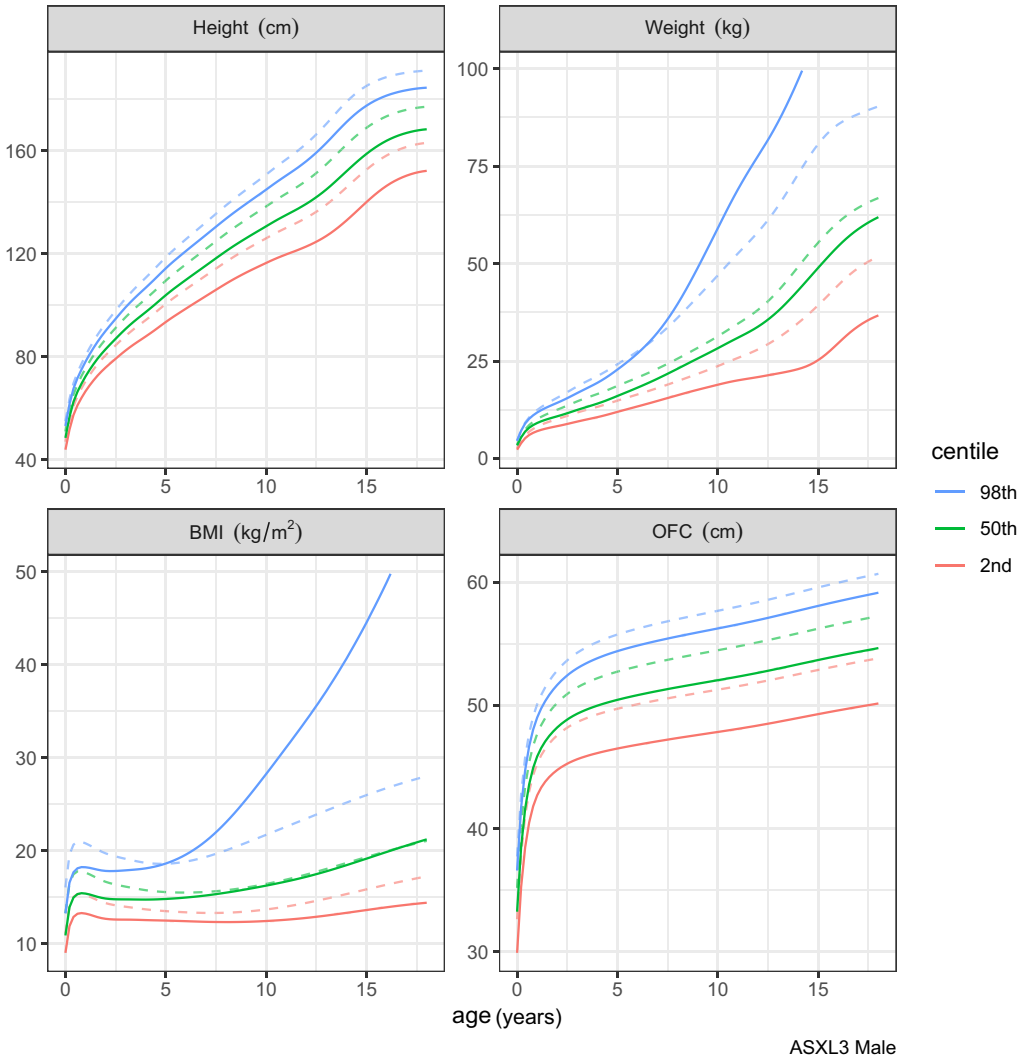

FIGURE 2 | *ASXL3*-specific measurement centiles for males. Corresponding British 1990 (UK90) centiles are shown as dashed curves.

may help providers reassure families and other subspecialists that the patient's growth fits what is expected for their genetic diagnosis and preclude unnecessary aggressive nutritional interventions and unnecessary surgical placement of feeding tubes.

Of note, these newly derived gene-specific growth charts are primarily based on data from the United Kingdom, with the second-largest contribution from the United States and smaller contributions from other countries. Users of these charts should consider potential country-specific and individual familial factors that may influence growth outcomes.

We recommend that growth in children with *ASXL3*-related disorder is evaluated with reference to these user-friendly condition-specific growth charts, in addition to population charts and while accounting for individual limitations and contextual factors. We recommend that all children with *ASXL3*-related disorder undergo routine growth monitoring, with clinical assessment for short stature and/or failure to thrive as indicated. These novel growth charts provide the most accurate approximation of expected growth for this rare genetic condition.

Acknowledgments

We are thankful for the individuals in the DDD study and *ASXL3* Natural History Study who consented to anonymized data sharing.

Funding

The authors have nothing to report.

Ethics Statement

The DDD study has UK Research Ethics Committee approval (10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC). All participants gave informed consent, as required by the REC. All published data were de-identified. Specific ethical approval for the growth charts development was given via a DDD Complementary Analysis Proposal Approval (CAP#371). The *ASXL3* Natural History Study, sponsored by Sheffield Children's Hospital and The University of Sheffield (UK), received REC (23/

SC/0151) and HRA approval on 2 June 2023. All participants enrolled in the study gave informed consent for anonymized data sharing to allow this work.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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