Development of a Klinefelter syndrome specific stature-for-age growth chart

Taylor E Marshall, MS; Laura Pyle, PhD; Anna Furniss, MS; Shanlee M Davis, MD, PhD

1University of Colorado School of Medicine, 2Department of Pediatrics, University of Colorado School of Medicine, 3Department of Biostatistics and Informatics, University of Colorado Anschutz Medical Campus, 4ACCORDS, University of Colorado Anschutz Medical Campus, 5eXtraOrdinaryY Kids Clinic, Children’s Hospital Colorado

BACKGROUND
- Klinefelter syndrome (KS) is a common genetic condition in males with an extra X chromosome (47,XXY)
- KS is associated with tall stature – expected adult height is 2-3 inches above mid-parental height
- Condition-specific growth charts for genetic disorders can assist with the assessment of pathologic growth
- A KS-specific growth chart does not exist

Aim: To generate a Klinefelter syndrome specific stature-for-age growth chart for males 2-20 years of age

METHODS
- Data were obtained from PEDSnet – a multi-institutional clinical research network

Inclusion Criteria
- Billing diagnosis of KS
- Male sex
- Age 2-20 years
- ≥ 1 outpatient visit between 2009-2019
- Age ≥ 2 years at first visit
- Age ≤ 18 years
- No sex change or gender dysphoria
- No other genetic diagnosis
- No diagnosis of difference in sex development
- No obesity
- No sedative or growth hormone therapy

Exclusion Criteria
- Other genetic diagnosis
- Diagnosis of difference in sex development
- Gender dysphoria
- Data Processing
- Outliers and duplicate height values were identified and cleaned with an exponentially weighted moving average (EWMA) based algorithm (R v4.2.1, growthclean) and individual review
- Statistical Analysis
- Effect of age on height was modeled using non-parametric quantile regression (R v4.2.1, quantregGrowth)
- Covariates – testosterone prescription, number of patient visits
- Percentiles – 5th, 10th, 25th, 50th, 75th, 90th, 95th
- Center for Disease Control (CDC) growth curves were included for reference

RESULTS
- 986 patients with KS had at least one usable height measurement (mean ± SD of 9.1 ± 10.6 measures per patient over 4.2 ± 3.7 years) between 2-20 years of age, yielding 8,936 total height measurements for this analysis

2 to 20 years: Klinefelter Syndrome Males Stature–for–age percentiles

The 95th (top left) and 50th (top right) percentile curves for KS are similar to the CDC reference initially; after 5 years and 9 years of age respectively, stature in KS at the 95th and 50th percentile is greater than the CDC reference.

The 5th percentile (bottom left) for KS is initially below the CDC 5th percentile, from 10-16 years of age the 5th percentile curve is transiently greater in KS than the CDC reference, and approaching final stature the KS 5th percentile is below the CDC 5th percentile

LIMITATIONS
- Model is unable to account for intra-individual height trajectory
- Selection bias for known KS
- EHR errors of omission / inclusion

FUTURE DIRECTIONS
- Height velocity, weight, and BMI-for-age KS-specific growth charts
- KS-specific growth charts for boys 0-2 years of age

CONCLUSIONS
- Boys with KS have unique growth trajectories compared to the CDC curves
- The KS curves all seem to lack the typical pre-pubertal slowing of growth velocity, as well as an obvious pubertal growth spurt
- Tall stature is not universal in KS, particularly in infancy and early childhood

IMPLICATIONS
- KS specific growth charts will be helpful in the clinical prediction of height potential, in facilitating discussions with families regarding expectations, and in identifying abnormal growth patterns that may warrant evaluation

ACKNOWLEDGEMENTS, FUNDING & DISCLOSURES
- Special thanks to Dr. Shanlee Davis – my wonderful mentor – and the eXtraOrdinaryY Kids research team and patients
- None of the authors have any disclosures
- Support received from the NICHD, R03HD102773
- Project was determined by COMIRB to be Non-Human Subjects Research

SUPPLEMENTARY MATERIAL
- The 95th (top left) and 50th (top right) percentile curves for KS are similar to the CDC reference initially; after 5 years and 9 years of age respectively, stature in KS at the 95th and 50th percentile is greater than the CDC reference.

- The 5th percentile (bottom left) for KS is initially below the CDC 5th percentile, from 10-16 years of age the 5th percentile curve is transiently greater in KS than the CDC reference, and approaching final stature the KS 5th percentile is below the CDC 5th percentile

- The model is unable to account for intra-individual height trajectory
- Selection bias for known KS
- EHR errors of omission / inclusion

- Height velocity, weight, and BMI-for-age KS-specific growth charts
- KS-specific growth charts for boys 0-2 years of age

- Boys with KS have unique growth trajectories compared to the CDC curves
- The KS curves all seem to lack the typical pre-pubertal slowing of growth velocity, as well as an obvious pubertal growth spurt
- Tall stature is not universal in KS, particularly in infancy and early childhood

- KS specific growth charts will be helpful in the clinical prediction of height potential, in facilitating discussions with families regarding expectations, and in identifying abnormal growth patterns that may warrant evaluation

- Special thanks to Dr. Shanlee Davis – my wonderful mentor – and the eXtraOrdinaryY Kids research team and patients
- None of the authors have any disclosures
- Support received from the NICHD, R03HD102773
- Project was determined by COMIRB to be Non-Human Subjects Research