

X-Linked Coffin-Lowry Syndrome

Phenotype Differences By Sex

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Objective

Current literature on Coffin-Lowry Syndrome (CLS) is reported as aggregate data of males and females. When phenotype is vastly different between the sexes, averaged data becomes inaccurate for all patients. We aimed to analyze early gender-based differences in growth parameters, musculoskeletal features, systemic complications, functional independence, and educational needs using data from a CLS natural history and patient registry.

Methods

Survey data from 43 of 62 registered (20 female, 23 male; 69% response rate) CLS patients were analyzed. Respondents represented 11 countries (United States, Australia, Canada, England, Thailand, South Africa, France, India, New Zealand, Romania, and Switzerland). Demographic, clinical, musculoskeletal, neurological, functional, and educational variables were stratified by sex. Descriptive statistics were used to evaluate patterns and differences.

Variables analyzed included:

- Growth parameters (height, weight)
- Maternal age at birth
- Mobility status and wheelchair use
- Ophthalmologic and auditory complications
- ENT complications and ear surgeries
- Respiratory and pulmonary complications
- Musculoskeletal abnormalities
- Spinal deformities
- Gastrointestinal onset
- Functional independence and self-care abilities
- Educational placement and support services

Descriptive comparisons were conducted between females and males. Given the sample size, analyses were exploratory and not powered for inferential statistical testing.

Results

Figure 1. Sex-stratified comparison of spinal deformities (raw counts). Males showed higher rates across all three measures, notably scoliosis (14 vs. 1) and lordosis, reported exclusively in males (7 vs. 0)

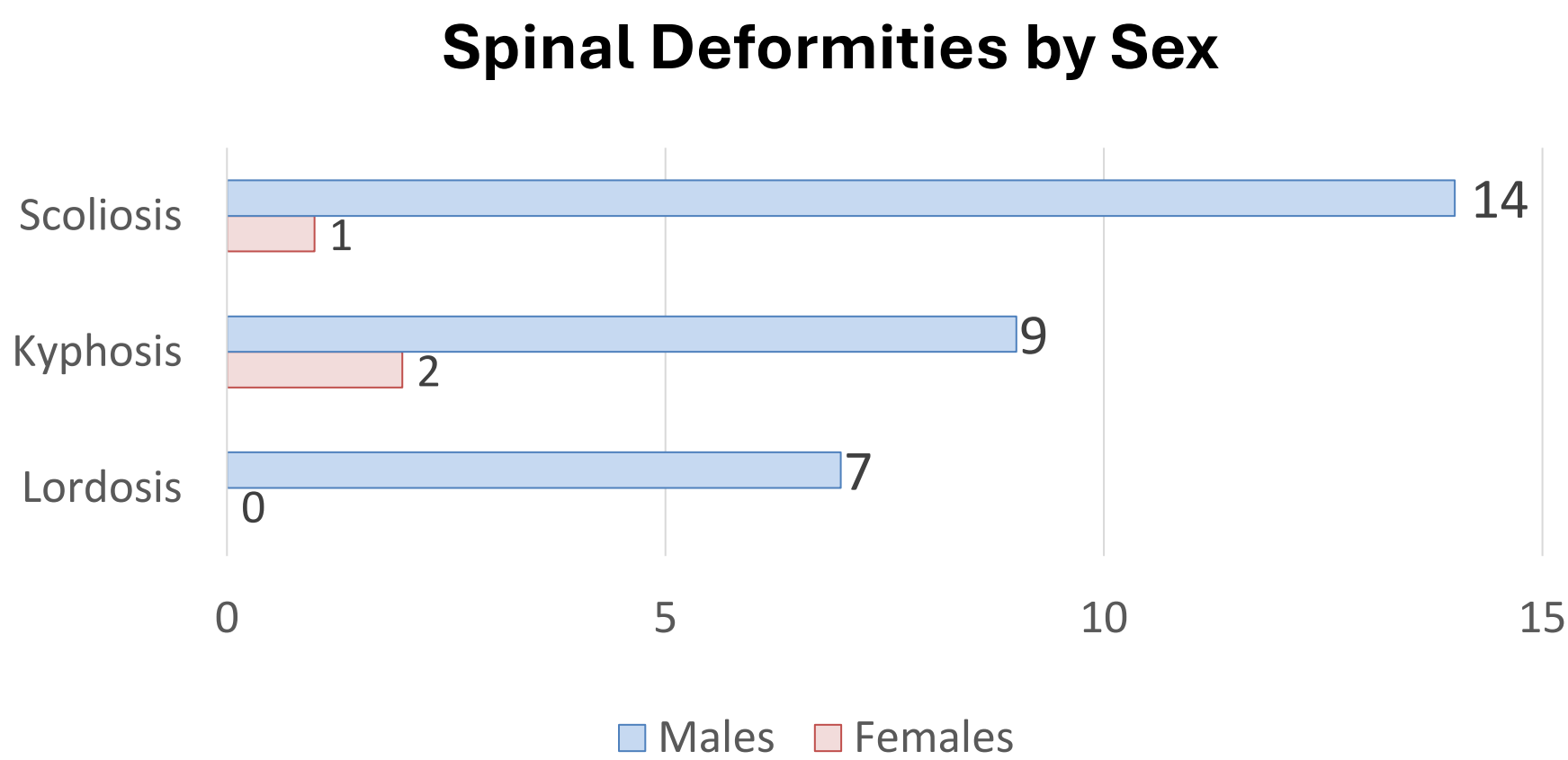


Figure 2. Mean age of gastrointestinal symptom onset by sex (years). Males presented with GI involvement approximately 11.6 years earlier than females on average.

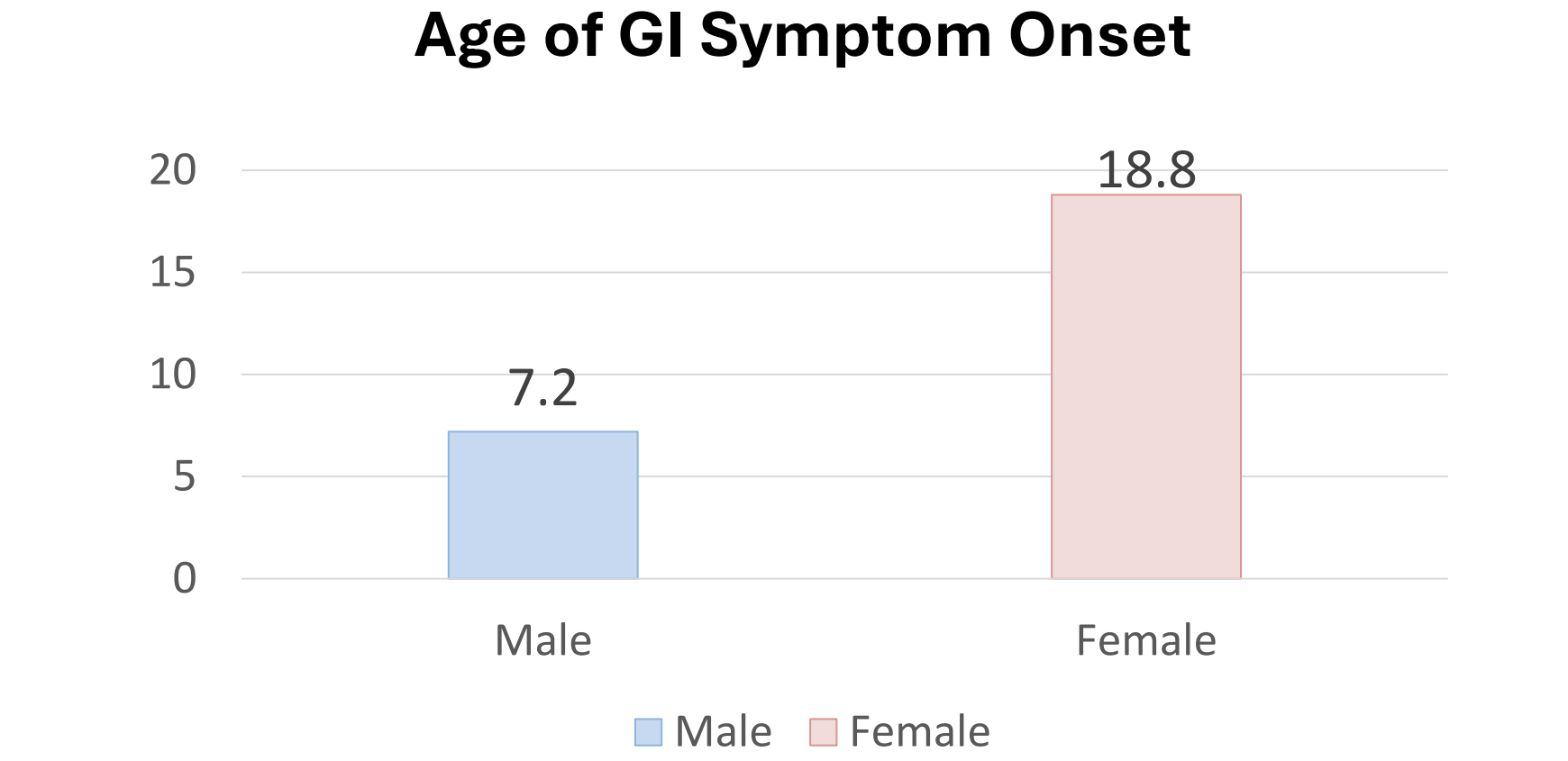


Figure 3. Wheelchair dependence by sex. Left: number of patients requiring wheelchair use (count). Right: mean age at wheelchair onset (years). Males were more than twice as likely to require a wheelchair and did so approximately 7 years earlier than females on average.

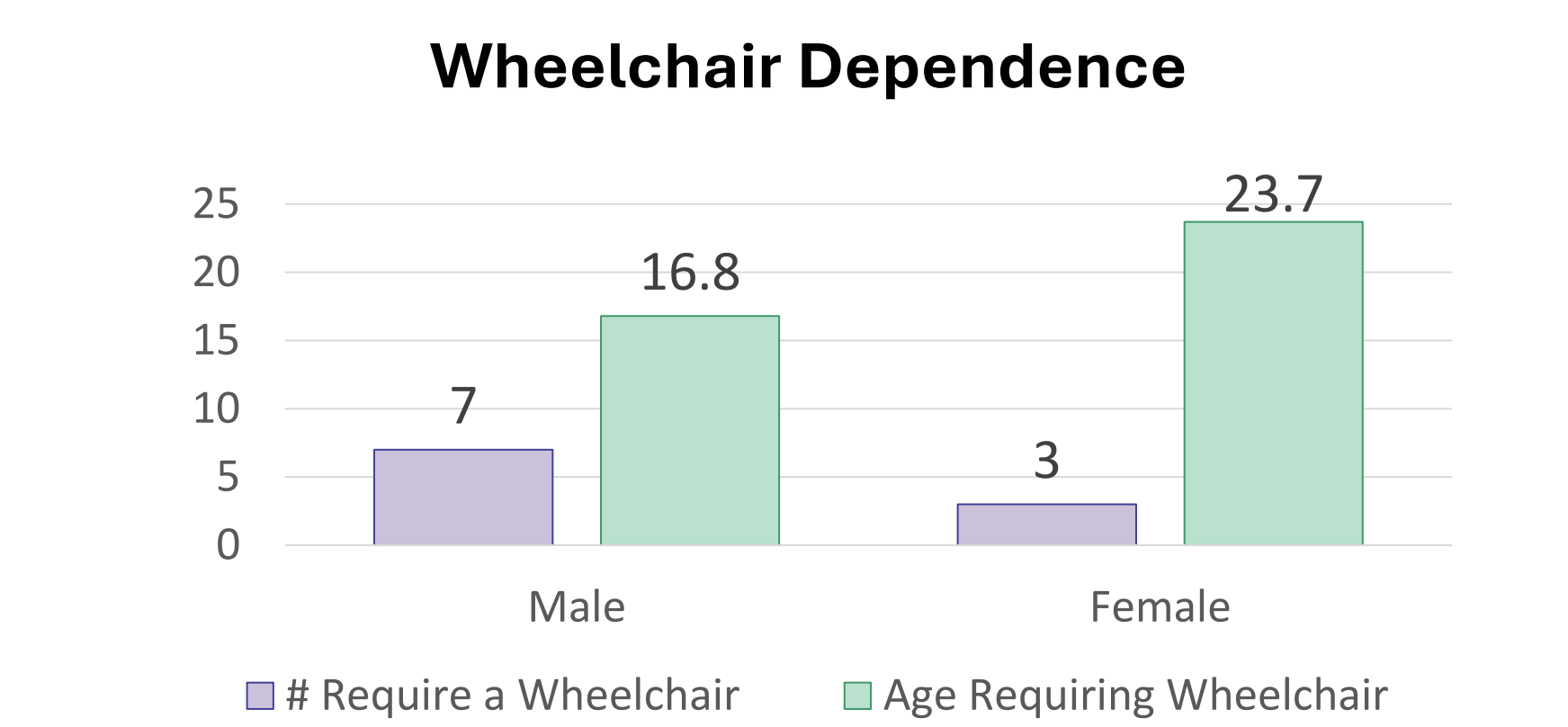


Figure 4. Sex-stratified comparison of average height, weight, and short stature prevalence. Males were taller on average but weighed less than females, despite a higher prevalence of short stature among males (14 vs. 10).

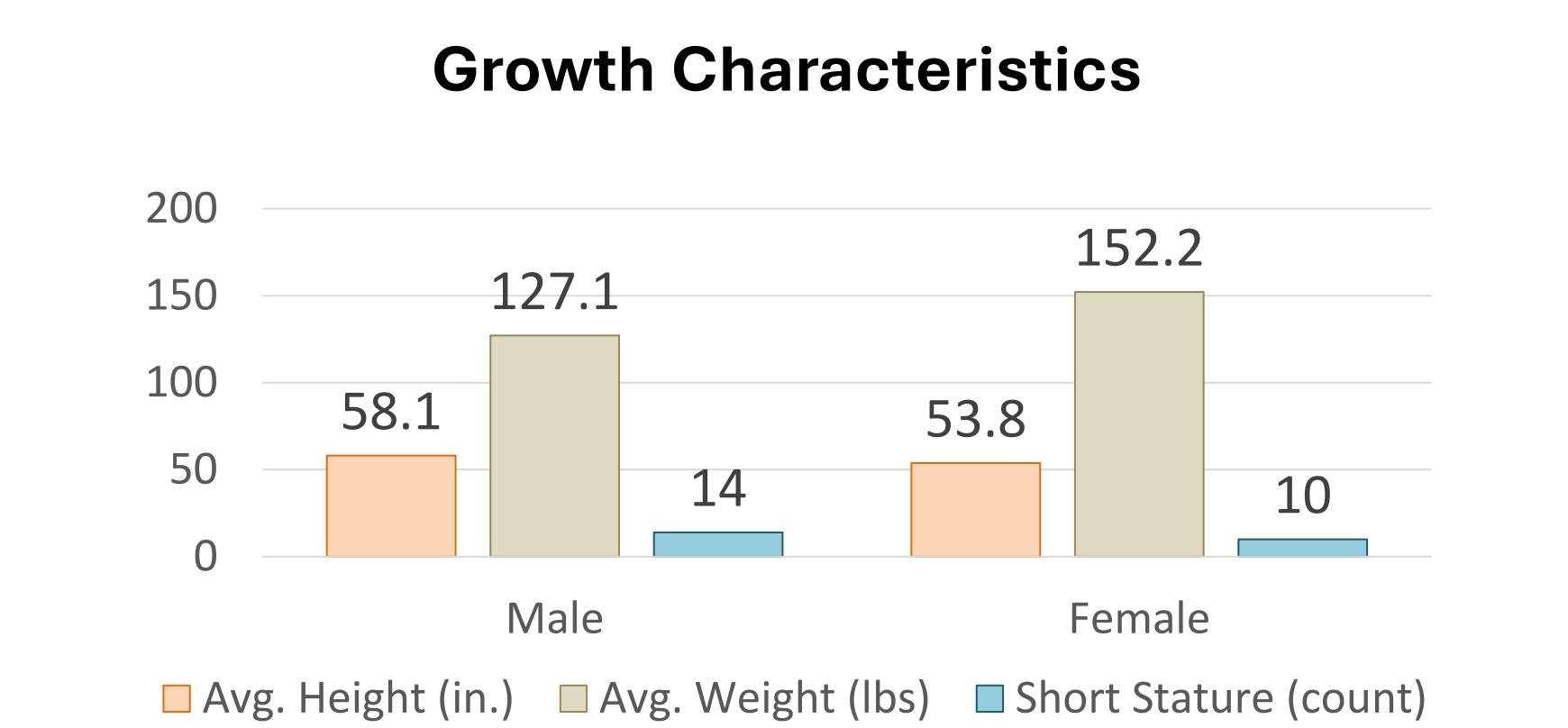


Figure 5. Sex-stratified comparison across respiratory, ENT, functional, and educational domains among CLS registry patients (raw counts). Color indicates direction of difference: blue = male-predominant, pink = female-predominant, gray = comparable between sexes.

Domain-Level Comparison of Clinical, Functional, and Educational Outcomes by Sex	
Domain	Findings
Musculoskeletal abnormalities (delayed fontanelle closure, bone age)	2x more frequent in males
Respiratory complications (asthma, frequent bronchitis, recurrent pneumonia)	~2x more frequent in males (11 vs. 6)
Recurrent ear infections	~2x more frequent in males (8 vs. 4)
Need for ear tubes	~2x more frequent in males (9 vs. 5)
Educational support (full-time 1:1 aide)	Greater need in males (7 vs. 1)
Functional independence (dressing, hygiene, bathing, food prep)	Greater in females
Dental issues	Comparable between sexes
Hearing loss	Comparable between sexes
Vision abnormalities	Comparable between sexes

Discussion

This early registry analysis suggests a pattern of greater clinical severity among males with CLS across multiple domains, consistent with the X-linked inheritance mechanism.

The most pronounced gender differences were observed in:

- Spinal deformities
- Respiratory complications
- Functional independence
- Educational intensity needs
- Age of gastrointestinal onset
- Age of wheelchair dependence

Spinal pathology appears to be a central driver of downstream complications, potentially contributing to respiratory compromise and earlier mobility decline.

Females, although affected, generally demonstrated:

- Later onset of systemic complications
- Lower rates of severe spinal deformity
- Greater preservation of independence
- Reduced need for intensive educational supports

Limitations

This exploratory registry analysis was limited by a small sample size and incomplete data for some outcomes. Registry-based data may be affected by recall, reporting, and ascertainment bias and analyses were not adjusted for age or duration of follow-up. Genotype-level factors and X-chromosome inactivation that may contribute to phenotypic variability in females were not evaluated.

Conclusions

Early registry data suggest that males with CLS experience greater clinical severity and earlier progression across multiple domains. These findings underscore the importance of gender-stratified monitoring protocols and support the need for longitudinal investigation to better understand disease progression and inform anticipatory clinical management.

References

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