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Targeted Gene Sequencing, Bone Health, and Body Composition in Cornelia de Lange Syndrome

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Abstract: The aim of this study was to evaluate bone health and body composition by dual-energy X-ray absorptiometry (DXA) in individuals with Cornelia de Lange Syndrome (CdLS). Overall, nine individuals with CdLS (five females, all Caucasian, aged 5–38 years) were assessed. Total body less head (TBLH) and lumbar spine (LS) scans were performed, and bone serum biomarkers were determined. Molecular analyses were carried out and clinical scores and skeletal features were assessed. Based on deep sequencing of a custom target gene panel, it was discovered that eight of the nine CdLS patients had potentially causative genetic variants in *NIPBL*. Fat and lean mass indices (FMI and LMI) were 3.4–11.1 and 8.4–17.0 kg/m^2, respectively. For TBLH areal bone mineral density (aBMD), after adjusting for height for age Z-score of children and adolescents, two individuals (an adolescent and an adult) had low BMD (aBMD Z-scores less than –2.0 SD). Calcium, phosphorus, 25-OH-vitamin D, parathyroid hormone, and alkaline phosphatase levels were 2.08–2.49 nmol/L, 2.10–3.75 nmol/L, 39.94–78.37 nmol/L, 23.4–80.3 pg/mL, and 43–203 IU/L, respectively. Individuals with CdLS might have normal adiposity and low levels of lean mass measured with DXA. Bone health in this population seems to be less of a concern during childhood and adolescence. However, they might be at risk for impaired bone health due to low aBMD in adulthood.

Keywords: Cornelia de Lange syndrome; *NIPBL*; body composition; bone; dual-energy X-ray absorptiometry

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1. Introduction

Brachmann de Lange syndrome and Cornelia de Lange syndrome (CdLS) were first described by Brachmann de Lange in 1916 [1] and Cornelia de Lange in 1933, respectively [2]. Advancement in scientific knowledge was rather scarce during the following decades, until

the 2000s, when research on CdLS grew exponentially [3–6]. Jackson et al. [7] reported that CdLS was slightly more common in females, but it affects men and women equally. It has been estimated the prevalence of CdLS is 1 case per 10,000–300,000 live births [3]. Therefore, CdLS is recognized as a rare disease.

CdLS is a consequence of spontaneous mutations in genes of the cohesion protein complex. *NIPBL* mutations are the most prevalent variants and occur in approximately 60–80% of cases [8–13]. To date, new advances in genomic techniques are making it possible for clinicians to improve the diagnosis of mutations in the known CdLS genes (*SMC1A, SMC3, RAD21, BRD4, HDAC8, ANKRD11,* and *MAU2*) [14–19], and other candidates are being proposed [20]. The CdLS phenotype is characterized as a spectrum because it includes individuals with the classic CdLS phenotypes (with scores $\geq$11 points), as well as individuals with nonclassic CdLS phenotypes (9–10 points), based on the first published international consensus on the diagnosis and management of CdLS [8].

Recent evidence [8] suggests that most people with CdLS present bone-related medical problems such as scoliosis or short stature. In addition, cardiovascular problems and intellectual disability, combined with limited physical activity [3] and restricted mobility, may harm the bone health and body composition of people with CdLS. However, the available scientific literature about body composition in these individuals is almost nonexistent. We found only two studies [7,21] reporting that 18–30% of adolescents and adults with CdLS were overweight. Previous studies used body mass index (BMI) to determine overweight and obesity; however, using the fat mass index (FMI) and lean mass index (LMI) provides an improvement, because BMI cannot distinguish between fat mass and lean body mass [22]. As far as we know, when assessing body composition and bone health in children and adolescents with CdLS, there are no data published with more complex techniques such as dual-energy X-ray absorptiometry (DXA). However, low bone density was described in a sample of 12 adults with CdLS [3]. Those authors pointed out that low bone density could be related to calcium or vitamin D deficiency and/or premature aging. They also emphasized that the relationship between bone density and fractures should be further investigated. For that matter, a study by Kline et al. [8] stated that no reliable studies on osteoporosis in CdLS are available.

Therefore, the primary objective of this study was to evaluate areal bone mineral density (aBMD) with serum biomarkers in individuals with CdLS. The secondary objective was to assess body composition in terms of fat and lean mass.

2. Materials and Methods

Participants: A total of 15 individuals with CdLS (10 females, all Caucasian, aged 5–38 years) participated in the present observational study with a case series design. Most of the individuals were referred by the Spanish Association of Cornelia de Lange Syndrome. They were evaluated by experienced clinicians in the field of CdLS. Clinicians reviewed medical records, took standard medical histories, and performed physical examinations to classify individuals following the international consensus criteria of CdLS [8]. A combination of cardinal and suggestive features was used to diagnose CdLS phenotypes. Classic phenotypes are indicated with a score of $\geq$11 points if at least 3 cardinal features are identified; a score of 9–10 indicates nonclassic phenotypes if at least 2 cardinal features are present. In addition, all individuals were subjected to molecular analysis using a custom targeted gene panel consisting of 35 CdLS-related genes via deep sequencing analysis based on Ion Chef and Ion S5 XL Systems (Thermo Fisher Scientific), as described previously [23], including *NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *HDAC8*, *BRD4*, *ANKRD11*, and *MAU2*.

Written informed consent was obtained from parents or guardians. The ethical guidelines for human research outlined by the Declaration of Helsinki (revision of Fortaleza 2013) [24] and the Declaration of Taipei [25] were followed. The protocol study was approved by the Ethics Committee of Clinical Research of the Government of Aragón (CEICA; PI16/225).

Measurements: Individuals with CdLS underwent anthropometric examination wearing no shoes and minimal clothing. Height was measured to the nearest 0.1 cm with a stadiometer (SECA 225, SECA, Hamburg, Germany) and weight to the nearest 0.1 kg with an electronic scale (SECA 861, SECA, Hamburg, Germany). BMI, FMI, and LMI were calculated as weight (kg) or fat mass (kg) or lean body mass (kg) divided by height squared (m^2). Anthropometric Z-scores were calculated based on Centers for Disease Control growth charts for children and adolescents age 2 to 20 years. FMI and LMI Z-scores were calculated based on the body composition reference values published by Hinton et al. [26].

Lumbar spine (LS) and total body less head (TBLH) bone mineral content (BMC) and aBMD were determined by means of DXA scan, evaluated with the pediatric version of QDR-Explorer software, version 12.4 (Hologic Corp., Bedford, MA, USA). All scans were performed by the same operator, who had been fully trained in the operation of the scanner, the positioning of subjects, and the analysis of scans according to the manufacturer's guidelines. Coefficients of variation for the DXA measurements in our laboratory have already been published [27], and were 2.3% for BMC and 1.3% for aBMD. Adjusted BMC and aBMD Z-scores, according to the reference values provided by Zemel et al. [28], were calculated.

Blood samples were collected and centrifuged, and serum was separated into aliquots in October (autumn). Levels of 25-OH-vitamin D, calcium, phosphorus, alkaline phosphatase (ALP), and parathyroid hormone (PTH) were measured by a commercially available kit using the Roche Cobas 6000 autoanalyzer (Roche Diagnostic, Mannheim, Germany). Levels of 25-OH-vitamin D and PTH were determined by electrochemiluminescence. Levels of calcium, phosphorus, and ALP were measured photometrically.

3. Results

After removing individuals with blurred or incomplete/unfinished DXA scans, 9 individuals (five females) out of the total sample of 15 individuals with CdLS were finally analyzed.

3.1. Clinical and Molecular Diagnosis

Based on their clinical scores, six individuals showed classic phenotypes and three showed nonclassic phenotypes; one had a clinical score of 7 points but a positive molecular diagnosis. Moreover, eight individuals had likely pathogenic variants in *NIPBL*, and the remaining individual had no genetic diagnosis based on *NIPBL* gene sequencing (Table 1).

3.2. Body Composition and Bone Health

Body composition parameters of the total sample are shown in Table 2. Two of six children and adolescents were considered to be underweight and one was at risk of overweight based on the percentile of BMI for age [29]. Similarly, two of three adults with CdLS were considered to be underweight and one at risk of overweight by BMI (according to World Health Organization BMI categories (18.5 to <25, 25 to <30, and $\geq$30 kg/m^2)). We also used FMI and LMI for a better understanding of body composition assessment of individuals with CdLS. One adolescent was classified as having high adiposity ($\geq$75th percentile) [30,31] and three adults were classified as having low adiposity (<25th percentile) [31]. Perhaps more importantly, seven out of nine had low levels of lean body mass (LMI < 25th percentile).

Table 3 shows the bone health parameters. For TBLH, when BMD Z-scores were adjusted for height for age Z-score of children and adolescents, only two of nine individuals (an adolescent and an adult) had low BMD (Z-score of −2.0 SD or lower). For LS, only one adult with CdLS felt into the low BMD category.

Table 1. Demographic, anthropometric, and clinical characteristics, affected genes, and clinical scores of individuals with Cornelia de Lange syndrome.

Individual	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
Age (years)	4.7	5.4	14.1	15.1	15.5	17.5	23.5	31.2	37.9
Gender	M	F	M	F	F	M	M	F	F
Tanner stage	I	I	I	V	V	V	V	V	V
Affected gene	*NIPBL*	*NIPBL*	*NIPBL*	*No genetic variant detected*	*NIPBL*	*NIPBL*	*NIPBL*	*NIPBL*	*NIPBL*
Variant type	frameshift	missense	nonsense		missense	missense	exon deletion	missense	missense
Clinical score [1]	13	9	15	11	7	14	13	9	12
Cardinal features (2 points each if present)									
Synophrys and/or thick eyebrows	+	+	+	+	+	+	+	+	+
Short nose, concave nasal ridge, and/or upturned nasal tip	+	-	+	-	+	+	+	-	+
Long and/or smooth philtrum	+	+	+	+	-	+	-	-	-
Thin upper lip vermilion and/or downturned corners of mouth	+	+	+	+	-	+	+	+	+
Hand oligodactyly and/or adactyly	-	-	-	-	-	-	-	-	-
Congenital diaphragmatic hernia	-	-	-	-	-	-	-	-	-
Suggestive features (1 point each if present)									
Global developmental delay and/or intellectual disability	+	+	+	+	+	+	+	+	+
Prenatal growth retardation (<2 SD) [2]	+	-	+	-	-	+	+	-	+
Postnatal growth retardation (<2 SD) [2]	+	-	+	+	-	+	+	+	+
Microcephaly (prenatally and/or postnatally)	+	-	+	+	-	+	+	+	+
Small hands and/or feet	+	-	+	+	-	-	+	-	-
Short fifth finger	-	+	+	-	+	+	+	+	+
Hirsutism	-	+	+	+	+	+	+	+	+

Light gray: children; gray: adolescents; dark gray: adults. [1] According to Kline AD, Moss JF, Selicorni A et al. (2018) Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet;19:649–666 [8]. [2] Based on Carrascosa A et al. (2011) Estudios españoles de crecimiento 2010. *Rev. Esp. Endocrinol. Pediatr. 2 Suppl (1)*, 59–62 [32].

Table 2. Body composition measurements of study sample.

Individual (Gender-Age (Years))	I (M-4.7)	II (F-5.4)	III (M-14.1)	IV (F-15.1)	V (F-15.5)	VI (M-17.5)	VII (M-23.5)	VIII (F-31.2)	IX (F-37.9)
Height (cm)	93.8	112.1	130.0	148.8	155.3	166.0	157.0	143.2	148.3
Height Z-score	–3.1	0.2	–3.9	–2.0	–1.0	–1.3	-	-	-
Weight (kg)	11.9	19.5	43.1	40.2	55.8	49.8	44.2	36.0	62.8
BMI (kg/m^2)	13.5	15.5	25.5	18.2	23.1	18.0	17.9	17.6	28.6
BMI Z-score [1]	–2.1	0.3	1.5	–0.7	0.8	–1.6	-	-	-
BMI percentile [1]	2	60	94	24	79	5			
FM (kg)	4.1	6.2	18.7	15.2	19.4	9.3	9.9	12.1	23.0
FM (%)	34.1	31.8	43.9	38.2	33.2	19.0	23.6	33.8	37.0
Trunk FM (kg)	1.3	2.0	8.4	6.0	7.7	3.2	4.0	4.6	12.2
Appendicular FM (kg)	2.2	3.5	9.6	8.5	10.8	5.3	5.2	6.7	10.0
Appendicular FMI (kg/m^2)	2.5	2.8	5.7	3.9	4.5	1.9	2.1	3.3	4.5
FMI (kg/m^2)	4.6	4.9	11.1	6.9	8.1	3.4	4.0	5.9	10.5
FMI classification [2]	Normal	Normal	High	Normal	Normal	Low	Low	Low	Normal
FMI Z-score [3]	0.02 †	–0.49 †	1.53	–0.15	0.21	–1.20	–1.07	–1.20	0.10
LM (kg)	7.4	12.5	22.8	23.2	36.9	38.0	30.4	22.3	37.2
LM (%)	62.3	64.4	53.3	58.4	63.4	77.1	72.3	62.6	59.9
Trunk LM (kg)	3.3	5.6	11.2	11.7	18.8	19.4	15.6	11.7	20.5
Appendicular LM (kg)	2.4	4.4	9.1	9.1	15.2	15.7	12.2	8.0	13.9
Appendicular LMI (kg/m^2)	2.7	3.5	5.4	4.2	6.3	5.7	4.9	3.9	6.4
LMI (kg/m^2)	8.4	9.9	13.5	10.6	15.4	13.8	12.3	10.9	17.0
LMI classification [2]	Low	Low	Low	Low	Normal	Low	Low	Low	Normal
LMI Z-score [3]	–3.66†	–2.06†	–1.63	–3.26	0.17	–2.47	–3.76	–3.69	0.41

Light gray: children; gray: adolescents; dark gray: adults. M, male; F, female; BMI, body mass index; FM, fat mass; FMI, fat mass index; LM, lean mass; LMI, lean mass index. Appendicular: sum of four limbs. [1] Relative to age, derived from Centers for Disease Control (CDC) growth data. [2] According to Ofenheimer A et al. (2020). Reference values of body composition parameters and visceral adipose tissue (VAT) by dual-energy X-ray absorptiometry (DXA) in adults aged 18–81 years—results from the LEAD cohort. European journal of clinical nutrition; 74(8):1181–91 [31]. [3] Based on Hinton J et al. (2017). Dual-energy X-ray absorptiometry body composition reference values of limbs and trunk from NHANES 1999–2004 with additional visualization methods. *PloS ONE* 12(3). † Compared with an 8-year-old individual [26].

Table 3. Bone health parameters of study population.

Individual (Gender-Age (Years))	I (M-4.7)	II (F-5.4)	III (M-14.1)	IV (F-15.1)	V (F-15.5)	VI (M-17.5)	VII (M-23.5)	VIII (F-31.2)	IX (F-37.9)
DXA									
TBLH									
Area (cm^2)	719.44	834.11	1013.08	1161.89	1507.52	1546.81	1300.78	1197.21	1412.68
BMC (g)	278.31	395.14	701.17	845.45	1465.79	1251.46	1158.35	858.36	1240.15
BMC for age Z-score adjusted for HAZ [1]	–0.9	–1.2	–0.4	–1.9	0.73	–2.28	-	-	-
BMD (g/cm^2)	0.387	0.473	0.692	0.727	0.972	0.809	0.890	0.716	0.877
BMD for age Z-score adjusted for HAZ [1]	–1.3	–1.2	–0.4	–1.7	1.2	–2.5	-	-	-
LS (L_1-L_4)									
Area (cm^2)	26.15	31.73	33.73	38.84	48.97	56.37	46.77	42.20	50.21
BMC (g)	10.56	14.72	24.22	35.37	56.04	48.61	46.89	32.53	55.09
BMC for age Z-score adjusted for HAZ [1]	0.2	–0.2	0.9	–0.5	1.2	–0.6	-	-	-
BMD (g/cm^2)	0.404	0.463	0.718	0.910	1.144	0.862	1.002	0.770	1.097
BMD for age Z-score adjusted for HAZ [1]	–0.1	–0.7	1.9	0.7	2.2	–0.5	-	-	-
Serum Biomarkers									
Calcium (nmol/L)	2.47	-	2.46	2.41	2.49	2.34	2.41	2.33	2.08
Phosphorus (nmol/L)	1.65	-	1.16	0.99	1.19	1.06	1.21	0.99	0.68
25-OH-vitamin D (nmol/L)	59.75	-	67.14	78.37	55.66	47.92	71.39	39.94	49.42
PTH (pg/mL) [2]	26.1	-	29.7	23.4	29.5	34.9	30.2	37.9	80.3
ALP (IU/L) [2]	-	-	203	108	129	110	135	43	60
Skeletal features									
Restricted mobility	No	No	No	No	No	No	No	No	No
Back pain	No	No	No	No	Yes	No	No	No	No
Scoliosis	No	No	No	Yes	No	No	No	No	No
Vertebral fracture	No	No	No	No	No	No	No	No	No
Other conditions	No	No	Flat feet hallux valgus	Claw feet	No	No	No	No	No
Treatments affecting bone metabolism									
Anticonvulsants	No	No	No	No	Levetiracetam Oxcarbazepine	No	No	No	No
Proton-pump inhibitors	Lansoprazole	No	Omeprazole	No	No	Omeprazole	No	No	No
Other treatments	No	No	Risperidone	No	No	Risperidone Sertraline hydrochloride	Risperidone	No	No

Light gray: children; gray: adolescents; dark gray: adults. DXA, dual-energy x-ray absorptiometry; TBLH, total body less head; BMC, bone mineral content; BMD, bone mineral density; HAZ, height for age Z-score; LS, lumbar spine; PTH, parathyroid hormone; ALP, alkaline phosphatase. [1] Based on Zemel B et al. (2011). Revised Reference Curves for Bone Mineral Content and Areal Bone Mineral Density According to Age and Sex for Black and Non-Black Children: Results of the Bone Mineral Density in Childhood Study. J Clin Endocrinol Metab, 96(10):3160–31. [2] Age-dependent reference values: calcium: 1–5 years: 2.35–2.69 nmol/L; 6–12 years: 2.35–2.57 nmol/L; adults (F) 2.2–2.5 nmol/L, (M) 2.27–2.54 nmol/L; phosphorus: 1–5 years: 1.45–2.10 nmol/L; 6–12 years: 1.16–1.87 nmol/L; 13–20 years: 0.74–1.45 nmol/L; 25-OH-vitamin D: ≥74.87 nmol/L; PTH: 10–65 pg/mL; ALP: children 150–600 IU/L, adults 60–170 IU/L.

Determination of calcium, phosphorus, 25-OH-vitamin D, PTH, and ALP levels was not possible for one child with CdLS due to inconvenience in the process of blood collection. For the remaining group, calcium, phosphorus, 25-OH-vitamin D, PTH, and ALP levels were 2.08–2.49 nmol/L, 2.10–3.75 nmol/L, 39.94–78.37 nmol/L, 23.4–80.3 pg/mL, and 43–203 IU/L, respectively. Considering that the normal ranges differ according to age and sex, only one adult with CdLS had hypocalcemia (calcium 2.08 nmol/L, normal range 2.2–2.5 nmol/L), hypophosphatemia (phosphorus 0.68 nmol/L, normal range 0.81–1.45 nmol/L), and a low level of ALP (43 IU/L, normal range 60 IU/L). Moreover, following international guidelines that classify serum concentrations of 25-OH-vitamin D values above 75 nmol/L as sufficient [33], seven individuals with CdLS were below this cut-off, and in only one of the oldest individuals the decrease was remarkable (39.94 nmol/L). Moreover, they also showed the lowest values of calcium, phosphorous, and ALP, accompanied by the highest values of PTH. Regarding the skeletal features or treatments affecting bone metabolism, none of the nine individuals had restricted mobility, used inhaled glucocorticoids, or took vitamin D supplements.

However, most of the individuals, except one, had gastroesophageal reflux, necessitating the use of proton pump inhibitors for 33.3% of them [3]. In our sample, only one participant was diagnosed with epilepsy and was using anticonvulsants (levetiracetam and oxcarbazepine) during the assessments. Nonetheless, this participant did not have significantly decreased levels of vitamin D (55.66 nmol/L) [34]. One individual was under treatment with sertraline and two with risperidone due to aggressive behavior. Regarding possible anomalies of the spine, only one adolescent with CdLS had low-grade scoliosis without requiring treatment at present, and another reported low back pain in isolation. Neither vertebral nor other fractures in any individual with CdLS were found, except for a patient who had suffered a humerus fracture caused by aggressive behavior.

4. Discussion

As far as we know, this is the first study to assess bone health, body composition, and serum bone biomarkers in a sample of individuals with CdLS. Furthermore, deep sequencing for a custom target gene panel consisting of 35 genes related to CdLS discovered causative genetic variants in NIPBL. Therefore, this study will provide useful information for doctors, researchers, and therapists working with them.

First, our sample consisted of children, adolescents, and adults, which can provide some information on the different evolutionary stages throughout the lives of people with CdLS. Although nine individuals may seem like a somewhat small number, our sample is quite similar to that of a study carried out by Kline et al., in which 14 adults with CdLS were evaluated by DXA [3]. Moreover, it is important to underline that the assessment of body composition by DXA in individuals with CdLS is challenging. They must be motionless for the necessary exploration time. It is also complicated by the intellectual disability they have and the gastroesophageal reflux that occurs in the supine position.

Previous studies described slow growth of CdLS individuals based on growth curves [3,35]. On the one hand, some adolescents with CdLS might be underweight; on the other hand, adolescents with CdLS can became overweight and develop obesity, which can be induced by high-calorie meals along with low levels of physical activity or psychotherapeutic treatment options [3].

Along this line, other studies [7,21] reported that between 18 and 30% of adolescents and adults with CdLS were overweight by BMI. BMI might not be accurate, because it could be masking important health-related body composition issues. Lean mass in growing individuals is related to growth as well as size. Thus, performing a more comprehensive body composition assessment with DXA allowed us to use other indices such as FMI and LMI. These variables improve on BMI by allowing for an independent assessment of fat and lean body mass. In addition, the ability to assess FMI and LMI independently and simultaneously is especially useful for children with chronic diseases [30]. Although seven out of nine individuals with CdLS had body fat percentages higher than 30%, despite some

being classified as underweight according to BMI, only one individual was classified as having high adiposity by BMI. In the remaining sample, five individuals were classified as having normal adiposity, and three as having low adiposity by FMI. Focusing on lean mass, seven out of nine individuals were classified as having low levels of lean body mass by LMI. These findings are especially important in CdLS individuals, because they might show that fat and lean body mass may be affected differently, and a "normal" BMI may conceal deficits in lean mass, as happened for participant III (cachectic obesity) [36]. Moreover, three individuals (VI, VII, and VIII) had low lean body mass and low adiposity, and at least two of them could be classified as sarcopenic [37,38]. This finding makes it reasonable to suppose that individuals with CdLS have low levels of lean mass in addition to slow growth and proportionate small stature [35]. Taking all of these factors into account—low levels of physical activity, low body weight, and low lean mass—according to Frost's mechanostat theory [39], even the youngest individuals with CdLS would be expected to have low bone mass.

In the present study, using DXA to measure aBMD, we show that two out of nine individuals had a TBLH aBMD Z-score less than 2.0 SD. Thus, they had low bone mineral mass according to the 2019 official Pediatric Positions of the International Society for Clinical Densitometry (ISCD) [40]. This document indicates that in children with short stature or growth delay, aBMD results should be adjusted by height Z-scores. In addition, the diagnosis of osteoporosis in children and adolescents should be made based on densitometry and the presence of a clinically significant fracture history [40]. Interpretations of our data should be performed with caution, because we did not perform lateral spine radiographs. Another important consideration is that three out of the nine used or had used proton pump inhibitors, and there has been emerging evidence showing a link between long-term proton pump inhibitor usage and bone health [41]. For all the reasons stated above, analyzing the calcium–PTH–vitamin D axis and ALP levels was imperative.

It was surprising to find that only in the oldest participant the decline in vitamin D levels was accompanied by a decrease in the level of calcium, which could induce a rise in PTH level. Future studies are needed to clarify this point. Particularly, there is a need to carry out other body composition studies in older individuals with CdLS, because in the above-mentioned situation, bone resorption is expected to increase and could lead to osteoporosis.

Regarding other treatments affecting bone, seizures are common in CdLS individuals, and the use of anticonvulsants may have an impact on bone health and vitamin D metabolism [3,8,42]. Only one individual (participant V) has epilepsy, currently under treatment with levetiracetam and oxcarbazepine. Despite that, her bone and vitamin D values seemed to not be affected. However, it is well known that epilepsy is a prevalent disorder in childhood and that classic antiepileptic drugs, such as phenobarbital and carbamazepine, are inducers of hepatic cytochrome P450 enzymes and can cause vitamin D deficiency [43–46]. Nonetheless, there are few studies on the effects of newer antiepileptic drugs like levetiracetam. A recent Spanish study in a pediatric population suggested there was vitamin D deficiency associated with treatment with the latest generation of antiepileptic drugs [34]. These discrepancies highlight the importance of accounting for these factors in future body composition studies.

This study had some limitations. It was a single-center study with a limited sample size. Moreover, comparisons between groups were not possible due to the lack of a control group; a normative dataset and Z-score values were used instead. In addition, it is important to acknowledge that CdLS is a rare disease. Importantly, as far as we know, this is the first study to document aBMD in some children and adolescents with CdLS.

In conclusion, individuals with CdLS might have normal adiposity by FMI and low levels of lean mass by LMI measured with DXA. Bone health in this population seems to not be as much of a concern during childhood and adolescence. However, these individuals might be at risk for impaired bone health due to low lean mass in adulthood. Accordingly,

more studies are needed to determine whether there is an increased risk of fracture or poor musculoskeletal outcomes associated with CdLS.

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Abbreviations

DXA	Dual-energy X-ray absorptiometry
CdLS	Cornelia de Lange syndrome
TBLH	Total body less head
LS	Lumbar spine
FMI	Fat mass index
LMI	Lean mass index
aBMD	Areal bone mineral density
BMI	Body mass index
SD	Standard deviation
M	Male
F	Female
FM	Fat mass
LM	Lean mass
HAZ	Height for age Z-score
PTH	Parathyroid hormone
ALP	Alkaline phosphatase

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