Tetrasomy 18p is a rare chromosomal abnormality, resulting from an additional iso-chromosome composed of two copies of the short arm. It is characterized by craniofacial abnormalities, neuromuscular dysfunction, and developmental delay. The Chromosome 18 Clinical Research Center has established the largest cohort of individuals with this rare genetic condition. Here, we describe a case series of 21 individuals with tetrasomy 18p who have a previously unreported clinical finding: low bone mineral density. Most individuals met criteria for low bone density despite being relatively young (mean age of 21 years). Clinicians providing care to individuals affected by Tetrasomy 18p should be aware of their increased risk for decreased bone density and pathological fractures.

KEYWORDS
bone health, chromosome 18, dual x-ray absorptiometry, low bone density, tetrasomy 18p

1 | INTRODUCTION

Tetrasomy 18p is a rare chromosomal abnormality occurring in approximately 1 per 625,000 births (Wellesley et al., 2012). It is caused by an additional iso-chromosome composed of two copies of the chromosome 18 short arm, resulting in four total copies of the short arm. Although the clinical features are variable, characteristic findings include craniofacial abnormalities, neuromuscular dysfunction, and skeletal malformations (Bawazeer et al., 2018). Individuals with tetrasomy 18p show signs of developmental delay and limitations in their speech and behavior (O'Donnell et al., 2015; Soileau et al., 2015). Almost all children and adults with tetrasomy 18p develop ambulatory skills at an average age of 33 months. (Sebold et al., 2015).

The Chromosome 18 Clinical Research Center is an international medical and educational resource for families and individuals diagnosed with alterations to their 18th chromosome. This Center has enrolled the largest number of individuals affected by these genetic anomalies. They collect extensive medical information, including diagnoses, laboratory analyses, and imaging studies through surveys, telephone conversations, and in-person interviews. Over the last few years, it has come to our attention that many young adult males with tetrasomy 18p have been diagnosed with and treated for low bone density. While decreased physical activity and height are major factors contributing to this potential finding, we sought to evaluate bone...
health in our cohort of patients with tetrasomy 18p. This observational study is clinically relevant as it reports data gathered from 21 study participants with tetrasomy 18p and presents bone imaging findings, serologic measures, and pertinent historical information.

2 | METHODS

2.1 | Study center and subjects

This study was conducted at The University of Texas Health Science Center in San Antonio, Texas (UTHSCSA). Permission was granted by the institutional review board at UTHSCSA and consent was obtained from families of all individuals participating in the study. All participants had their diagnosis of tetrasomy 18p confirmed via high resolution microarray analysis with regions of recombination at the centromere—a region between nucleotides 15,315,187 and 16,793,854 (Sebold et al., 2010). The study participants are enrolled in longitudinal research through the Chromosome 18 Clinical Research Center and were given the option to participate in this study. Data was collected through multiple sources, including medical charts, family questionnaires, mailed surveys, and electronic correspondence between families and the investigative team. Variables of interest included measures known to evaluate and affect bone health: dual energy x-ray absorptiometry (DXA) results, fracture history, degree of mobility, medications, serologic analytes, and anthropometrics.

2.2 | DXA measurements and anthropometrics

Participants' DXA reports for femoral neck, total hip, and lumbar spine L1–L4 bone measures were obtained from the family or primary care physician. Bone mineral content (g), bone mineral density (g/cm²), and Z-scores were provided. A Z-score of zero was equivalent to the mean, whereas a score between −1.0 and +1.5 was equivalent to values of one standard deviation below and 1.5 standard deviations above the mean, respectively. Per the International Society for Clinical Densitometry, a Z-score less than or equal to negative 2.0 is defined as "low bone mass or low bone mineral density for age" in individuals younger than 50 years. Weight and height were obtained at birth and at time of DXA evaluation. These anthropometric measures will be reported as Z-scores.

2.3 | Biochemical indices of bone health

Serologic measures collected were calcium, phosphorus, 25-OH vitamin D, parathyroid hormone, alkaline phosphatase, and thyroid function tests. Being a retrospective study, the timing of laboratory results was variable. We chose to include lab values obtained within a 90-day window from the DXA evaluation.

2.4 | Pertinent history affecting bone health

Medications known to impact bone health were included in the survey, as all current and previous medication history are maintained within our database of participants. We asked families to provide a history of bone fractures, bony abnormalities and ambulatory status.

2.5 | Statistical analysis

Continuous data was analyzed using Student’s t test, and categorical data was analyzed using Fisher’s exact test where appropriate. A p value ≤ .05 was considered statistically significant. STATA v.13 (Microsoft Corporation™, College Station, Texas) was used to analyze data.

3 | RESULTS

3.1 | Subjects

Twenty-one participants from the Chromosome 18 Clinical Research cohort provided DXA scan results for this study. Their ages at the time of their DXA scan ranged from 14 months to 49 years of age, with both genders equally represented. Males (n = 11) had an average age of 25.4 ± 11.6 years at time of DXA imaging, while females were scanned on average at a younger age (17.6 ± 10.5 years). Overall, the group of participants had a lower height when compared to healthy age and gender matched individuals. The demographic data is summarized in Table 1.

3.2 | Bone health

Among the 21 participants, 67% (n = 14) had a history of bone fracture(s), of which 50% (n = 7) had more than three fractures in their lifetime. Seven males (64%) and 6 females (60%) have a diagnosis of scoliosis, with 24% of participants experiencing a moderate to severe scoliosis. Refer to Table 2. Excluding the 14 month old, only two of the other 20 participants were not ambulatory: one at age 37 and the other at age 8.

3.3 | DXA measurements

While all included 21 participants had DXA scans, some did not have hip measurements, as they were too young. Others did not have their lumbar spine measurements due to their degree of scoliosis or kyphosis. The lumbar spine bone mineral density (BMD) values in

| TABLE 1 | Participant demographics |
| --- | --- | --- |
| | Male | Female | Total group |
| Age at scan, years (mean, SD) | 25.4 ± 11.6 | 17.6 ± 10.5 | 21.7 ± 11.5 |
| Birth weight, Z-score (mean, SD) | −0.64 ± 1.01 | −0.97 ± 0.68 | −0.80 ± 0.86 |
| Birth length, Z-score (mean, SD) | 0.18 ± 1.64 | −0.50 ± 1.02 | −0.16 ± 1.37 |
| Height, Z-score (mean, SD) | −0.90 ± 1.12 | −1.64 ± 1.30 | −1.25 ± 1.24 |
| Weight, Z-score (mean, SD) | −0.88 ± 1.36 | −0.83 ± 1.64 | −0.85 ± 1.47 |
| BMI Z-score (mean, SD) | −1.10 ± 1.84 | −0.4 ± 1.57 | −0.70 ± 1.70 |
| Ambulating, number (%) | 9 (82%) | 9 (100%)<sup>a</sup> | 18 (90%)<sup>a</sup> |

<sup>a</sup>14 month old removed from ambulating calculations.
TABLE 2  Variables known to evaluate and affect bone health

<table>
<thead>
<tr>
<th>Fracture history (number, %)</th>
<th>Male n = 11</th>
<th>Female n = 10</th>
<th>Total group n = 21</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture number, (mean, SD)</td>
<td>1.5 ± 1.7 1.9 ± 2.1 0.35 ± 1.9</td>
<td>0.67</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Scoliosis (number, %)</td>
<td>7 (64%) 6 (60%) 13 (62%)</td>
<td>0.01</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Kyphosis (number, %)</td>
<td>7 (64%) 1 (10%) 8 (38%)</td>
<td>0.01</td>
<td>0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>Arthritis (number, %)</td>
<td>1 (9%) 0 1 (5%)</td>
<td>0.01</td>
<td>0.86</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Comparison between gender.  
** Number of participants (n) varies due to data availability given retrospective nature of study.

Males with DXA measurements were 0.82 ± 0.19 g/cm² (n = 9) and were 0.68 ± 0.25 g/cm² (n = 8) in females. The lumbar spine Z-score (n = 17) was −2.0 ± 1.2. Data is displayed in Tables 3–5. When taking all sites into consideration, the average lowest Z-score in all participants was −2.9 ± 1.8 with a range of −1.1 to −7.8.

3.4 Biochemical indices

Serum measurements for parathyroid hormone and phosphorus, (n = 7), calcium (n = 8), and alkaline phosphatase, thyroid stimulating hormone, and 25-OH vitamin D (n = 9) were obtained within close proximity to their DXA scans. With the exception of 25-OH vitamin D levels, the mean value of the bone analytes was within normal limits. The average 25-OH vitamin D was 30 ± 10 ng/dL (Table 6). Five participants (56%) had vitamin D levels consistent with insufficiency defined as a level <32 ng/dL (Alshahrani & Aljohani, 2013).

3.5 Medication history

Slightly more than a quarter (29%) of participants are currently on or have a history of chronic exposure to medications known to reduce bone density or increase the risk of fracture. These medications include seizure medications (Depakote-Divalproex Sodium; Ethosuximide: Trileptal-Oxcarbazepine; Lamictal-Lamotrigine); Proton Pump Inhibitors (PPI’s; Prevacid-Lansoprazole; Omeprazole); SSRI’s (Zoloft-Lamotrigine; Trileptal-Oxcarbazepine; Lamictal-Lamotrigine); Proton Pump Inhibitors (PPI’s; Prevacid-Lansoprazole; Omeprazole); SSRI’s (Zoloft-Lamotrigine; Trileptal-Oxcarbazepine; Lamictal-Lamotrigine). Nine participants (43%) are actively receiving mineral supplementation with calcium and vitamin D, whereas 3 (14%) were on bone-stabilizing medications (i.e., bisphosphonates: IV Pamidronate; Zoledronic Acid-Reclast; Actonel-Risedronate).

TABLE 3  Left femoral neck DXA measures

<table>
<thead>
<tr>
<th>Left femoral neck</th>
<th>Male n= 9</th>
<th>Female n= 4</th>
<th>Total n= 13</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD (g/cm²)</td>
<td>0.68 ± 0.13</td>
<td>0.49 ± 0.21</td>
<td>0.62 ± 0.17</td>
<td>0.06</td>
</tr>
<tr>
<td>BMD Z-score</td>
<td>−2.5 ± 0.70</td>
<td>−3.6 ± 2.9</td>
<td>−2.9 ± 1.8</td>
<td>0.25</td>
</tr>
<tr>
<td>BMC (g)</td>
<td>4.0 ± 0.70</td>
<td>2.1 ± 2.0</td>
<td>3.5 ± 1.3</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Abbreviations: BMC = bone mineral content (g); BMD = bone mineral density (g/cm²).

* Comparison between gender.  
** Number of participants (n) varies due to data availability given retrospective nature of study.

3.6 Pretreatment and posttreatment Z-scores

Figures 1 and 2 depict yearly DXA scans for two individuals treated with bisphosphonates, vitamin D, and calcium.

4 DISCUSSION

Decreased bone mass in individuals with tetrasomy 18p has not been previously reported.

The present study suggests that individuals with tetrasomy 18p have significantly lower bone density than healthy age and gender matched individuals. The reported disparity in Z-scores substantiates the theory that decreased bone mass in this population is multifactorial, likely secondary to decreased physical activity, use of osteolytic medications, and potentially, genetic influences. Given the observational nature of this study, no causative links can be made. However, this study highlights the poor bone health and associated comorbidities seen in this population.

The participant’s height, weight, and age, at the time of their DXA scan was accounted for in our Z-score calculations. The onset of puberty in those with tetrasomy 18p appears to occur at a similar age as unaffected individuals. (Sebold et al., 2010). As the presented Z-scores are standardized for age, they account for approximate pubertal status and affiliated hormone levels. Our study did not obtain a dietary history; however, we did capture a crude assessment of nutritional status via vitamin D serum levels. By accounting for anthropometrics, biochemical markers, and pubertal status, this study strengthens the hypothesis that decreased bone mineral density in individuals with tetrasomy 18p has a multifactorial etiology. Scoliosis (n = 13) and kyphosis (n = 8) were noted in a high percentage of participants at 62% and 38%, respectively. Studies have established a link between low bone density and scoliosis in adolescents (Chiru, 2011). Chiru et al. demonstrated that serum levels of receptor activator of nuclear factor-kB ligand, a potent inductor of bone resorption, were elevated in adolescents affected by scoliosis compared to the control population. Similar studies have shown positive correlation between low BMD and kyphosis in elderly populations (Thevenon et al., 1987). There are other factors that may contribute to the prevalence of spinal deformities in this population. Studies have demonstrated that neuromuscular diseases resulting in hypotonia or contracture can cause scoliosis and kyphosis (Vialle et al., 2013). Based on current literature, it seems plausible that neuromuscular pathologies in conjunction with premature low bone density contribute to the pervasiveness of scoliosis and kyphosis in this population.
Identifying a specific gene or genes as a potential cause of low bone mineral density in people with tetrasomy 18p is challenging. The highest bone density in our study cohort was a Z-score of $-1.1$, and even the youngest participant at age 14 months had an abnormally low BMD. The premature presentation and severity of low bone density observed in this study strengthen the likelihood of a multifactorial

### TABLE 4  Total left hip DXA measures

<table>
<thead>
<tr>
<th>Total left hip</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD (g/cm²)</td>
<td>8</td>
<td>4</td>
<td>12</td>
<td>0.07</td>
</tr>
<tr>
<td>BMD Z-score</td>
<td>8</td>
<td>5</td>
<td>13</td>
<td>0.47</td>
</tr>
<tr>
<td>BMC (g)</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: BMC = bone mineral content (g); BMD = bone mineral density (g/cm²).

<sup>a</sup> Number of participants (n) varies due to data availability given retrospective nature of study.

### TABLE 5  Lumbar spine DXA measures

<table>
<thead>
<tr>
<th>Lumbar spine L1-L4</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD (g/cm²)</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>0.24</td>
</tr>
<tr>
<td>BMD Z-score</td>
<td>9</td>
<td>9</td>
<td>18</td>
<td>0.53</td>
</tr>
<tr>
<td>BMC (g)</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Abbreviations: BMC = bone mineral content (g); BMD = bone mineral density (g/cm²).

<sup>a</sup> Number of participants (n) varies due to data availability given retrospective nature of study.

### TABLE 6  Biochemical indices

<table>
<thead>
<tr>
<th>Serum marker</th>
<th>n</th>
<th>Mean, SD</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>8</td>
<td>8.7 ± 2.6</td>
<td>8.5–10.2 mg/dL (Goldstein, 1990)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>7</td>
<td>3.2 ± 1.2</td>
<td>3.0–4.5 (Yu &amp; Lee, 1987)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>9</td>
<td>148 ± 83</td>
<td>56–170 U/L (male and female adults; Eastman &amp; Bixler, 1977)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mU/L)</td>
<td>9</td>
<td>2.4 ± 0.7</td>
<td>0.4–4.3 (Fontes, Coeli, Aguiar, &amp; Vaisman, 2013)</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td>7</td>
<td>27 ± 15</td>
<td>10–65 (Pagana &amp; Pagana, 2006)</td>
</tr>
<tr>
<td>25-OH vitamin D (ng/mL)</td>
<td>9</td>
<td>30.4 ± 9.8</td>
<td>32–90 (Alshahrani &amp; Aljohani, 2013)</td>
</tr>
</tbody>
</table>

Abbreviations: BMC = bone mineral content (g); BMD = bone mineral density (g/cm²).

Identifying a specific gene or genes as a potential cause of low bone mineral density in people with tetrasomy 18p is challenging. The highest bone density in our study cohort was a Z-score of $-1.1$, and even the youngest participant at age 14 months had an abnormally low BMD. The premature presentation and severity of low bone density observed in this study strengthen the likelihood of a multifactorial

![FIGURE 1  Pretreatment and posttreatment lumbar BMD Z-scores in five participants](Color figure can be viewed at wileyonlinelibrary.com)
etiology with synergistic effect. General frailty and limited mobility remain the key culprits, but there may be genetic factors contributing as well.

We include a gene of interest on chromosome 18p in support of the theory that genetics contribute to the poor bone health seen in this population. Since these data are from association studies they do not prove causation, but they provide clues as to potential relevant loci.

FAM210A gene (18:13,663,346-13,726,591), a nuclear-encoded mitochondrial protein. It has been linked to bone mineral density and risk of fracture (Estrada et al., 2012), to heel bone mineral density (Kemp et al., 2017), and to osteoporosis (Guo et al., 2011).

Half of the participants with 25-OH vitamin D levels measured were borderline deficient. Weaver et al. (2016) demonstrate that calcium and vitamin D supplementation is an approach that reduces fracture risk. Older adults with osteoporosis unresponsive to dietary supplementation are considered candidates for bisphosphonate therapy (Cosman et al., 2014). See Figures 1 and 2 for data delineating positive response to vitamin D, calcium, and bisphosphonate therapy in two individuals with tetrasomy 18p. Both had improved lumbar BMD Z-scores after treatment.

An important limitation of this case series is its small sample size. Data from a larger population of tetrasomy 18p individuals should be examined to strengthen the statistical significance of this study’s findings. Additionally, 29% of the participants reported chronic exposure to medications known to decrease bone mineral density or increase risk of fracture. The potential skewing effect of this confounding variable can be reduced with future studies of larger sample size. Furthermore, biochemical data were only available for some of the participants. Lastly, as an observational study, our data cannot establish a causative relationship between chromosomal defects and increased fracture risk. The aforementioned limitations notwithstanding, this case series presents previously unreported, statistically significant data that individuals with tetrasomy 18p have decreased bone mass.

### CONCLUSION

Our study provides evidence that individuals with tetrasomy 18p have lower than normal BMD. As this is the first study reporting DXA measures in people with tetrasomy 18p, further studies are needed to determine if these findings are isolated to tetrasomy 18p or whether they also affect individuals with other chromosome 18 abnormalities. Clinicians should be aware that individuals with tetrasomy 18p are at high risk for low bone mass and subsequent fractures.

### ACKNOWLEDGMENTS

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### CONFLICT OF INTEREST

None.

### FUNDING INFORMATION

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### REFERENCES

Fontes, R., Coeli, C. R., Aguiar, F., & Vaisman, M. (2013). Reference interval of thyroid stimulating hormone and free thyroxine in a reference population over 60 years old and in very old subjects (over 80 years): Comparison to young subjects. Thyroid Research, 6, 13.


