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LRP6 High Bone Mass Characterized in Two Generations Harboring a Unique Mutation of Low-Density Lipoprotein Receptor-Related Protein 6

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ABSTRACT
Osteoblast Wnt/β-catenin signaling conditions skeletal development and health. Bone formation is stimulated when on the osteoblast surface a Wnt binds to low-density lipoprotein receptor-related protein 5 (LRP5) or 6 (LRP6), in turn coupled to a frizzled receptor. Sclerostin and dickkopf1 inhibit osteogenesis if either links selectively to the first β-propeller of LRP5 or LRP6, thereby disassociating these cognate co-receptors from the frizzled receptor. Sixteen heterozygous mutations identified since 2002 within LRP5 and three heterozygous mutations identified since 2019 within LRP6 prevent this binding of sclerostin or dickkopf1 and account for the exceptionally rare, but highly instructive, autosomal dominant disorders called LRP5 and LRP6 high bone mass (HBM). Herein, we characterize LRP6 HBM in the first large affected family. Their novel heterozygous LRP6 missense mutation (c.719C>T, p.Thr240Ile) was present in two middle-aged sisters and three of their sons. They considered themselves healthy. Their broad jaw and torus palatinus developed during childhood and, contrary to the two previous reports of LRP6 HBM, the appearance of their adult dentition was unremarkable. Skeletal modeling, defined radiographically, supported classification as an endosteal hyperostosis. Areal bone mineral density (g/cm²) of the lumbar spine and total hip featured accelerated increases reaching Z-scores of ~+8 and +6, respectively, although biochemical markers of bone formation were normal. © 2023 The Authors. JBMR Plus published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

KEY WORDS: BONE DENSITY; BONE MODELING; DICKKOPF1; DXA; ENDOSTEUM; EXOSTOSIS; HYPEROSTOSIS; HYPODONTIA; LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN; LRP4; LRP5; LRP6; METABOLIC BONE DISEASE; OLIGODONTIA; OSTEOLAST; OSTEOMATOSIS; OSTEOPETROSIS; OSTEOSCLEROSIS; SCLEROSTIN; SKELETAL DYSPLASIA; SOST; TORUS PALATINUS; WNT; B-CATENIN

Introduction

Prominent among the rare Mendelian disorders manifesting generalized osteosclerosis and hyperostosis are the osteopetroses characterized over the past century and LRP5 and LRP6 high bone mass (HBM) recognized recently. The osteopetroses feature impaired osteoclast-mediated skeletal resorption and are caused by loss-of-function mutations of genes necessary for osteoclast formation or action. Consequently, osteopetrotic bones fail to remodel, have poor quality, and often fracture. In contrast, HBM features enhanced osteoblast-mediated bone formation caused by selective heterozygous mutations of LRP5 or LRP6 that alter the function of their encoded proteins, low-density lipoprotein receptor-related protein 5 (LRP5) and 6 (LRP6), respectively. On the osteoblast surface, when a Wnt couples to either of these cognate co-receptors complexed with a frizzled receptor, canonical Wnt/β-catenin signaling increases and generates good-quality bone. Physiologic inhibition of LRP5 or LRP6 occurs if either sclerostin or dickkopf1 binds to its first β-propeller, thereby disassociating it from the frizzled receptor. This inhibition is lost if the β-propeller is defective. Despite the contrasting pathogenesis underlying the
osteopetroses versus LRP5 HBM or LRP6 HBM, encasement of teeth as well as compression of the brain and one or more cranial nerves are potential complications from the excessive bone.\(^2,4\)

LRP6 HBM was first identified in 2019, and only two small families\(^{12}\) and one sporadic occurrence\(^{13}\) are reported. Herein, we characterize LRP6 HBM affecting five people in two generations of a Māori family in New Zealand who carry a unique fourth LRP6 defect.

**Subjects and Methods**

The proposita was incidentally discovered at age 43 years to have generalized osteosclerosis and hyperostosis consistent with a heritable bone disorder. Her sister and their five children then underwent evaluation (see Results), revealing five affected individuals, ie, the two sisters and three of their sons (Fig. 1).

The electropherograms distinguish the LRP6 missense mutation. Co-segregation analysis supported the LRP6 defect as pathogenic (\(p < 0.0008\)).

**Proposita**

The proposita (I-1: Fig. 1) presented with a 10-month history of neuralgic pain in her neck and right arm. Radiological studies (see below) revealed a dense skeleton. Magnetic resonance imaging (MRI) demonstrated spinal stenosis from disk prolapse at cervical vertebrae 5/6 and 6/7. Computed tomography (CT) showed generalized hyperostosis of the skull and facial bones. No intracranial pathology or cranial nerve compression was apparent. Surgical decompression of the prolapsed disks improved her symptoms, but disk or bone histology was not undertaken. She had fractured her left distal radius, including its growth plate, with significant trauma at age 9 years. After several weeks of casting, the wrist grew asymmetrically. Its alignment was improved by surgery at age 19 years. Trauma also explained her tooth loss. For many years, there had been intermittent headaches. Two years earlier, she had complained of achy knees and hands and a possible diagnosis of rheumatoid arthritis had been considered. Antinuclear antibodies were present in low titer; other serologies were negative. She and her elder affected nephew (II-4; Fig. 1) said they cannot float, and instead “sink.” She recalled no previous mention of dense bones.

Her height was 160 cm (63 inches), weight 65 kg (143 lbs), and body mass index (BMI) 25.4 k/m\(^2\). She had a broad jaw (Fig. 2) and large palatal torus (Fig. 3) but no other exostoses. Her left forearm was mildly deformed. Cranial nerve examination was normal, but audiometry was not performed.

Because her family seemed well and all would undergo (see below) dual-energy X-ray absorptiometry (DXA) screening (GE Lunar DPX, Madison, WI, USA), only she was evaluated with a radiographic skeletal survey. It revealed diffuse osteosclerosis and endosteal hyperostosis (Fig. 4).

DXA showed areal (g/cm\(^2\)) bone mineral density (aBMD) in her L1 to L4 spine 2.107 g/cm\(^2\) (\(Z\)-score + 7.7); left total hip 1.849 g/cm\(^2\) (\(Z\)-score + 6.9); and left femoral neck 1.725 g/cm\(^2\) (\(Z\)-score + 5.1), respectively; ie, 79%, 90%, and 84% above mean aBMD for age-matched women.

**Family study**

After genetic analyses that revealed the proposita’s LRP6 HBM (see below), six additional family members (Fig. 1) were screened for this diagnosis during a single outpatient visit, which included routine clinical, biochemical, and DXA assessments, and leukocyte DNA acquisition for LRP6 mutation analysis (see below). A radiograph of II-3, from age 6 years,
showed mild osteosclerosis (Fig. 4). Reportedly, the proposita’s mother had torus palatinus.

### Mutation analyses

Initially, the proposita’s leukocyte DNA was evaluated for diagnosis in a commercial laboratory (Blueprint Genetics, Seattle, WA, USA) using version 3 of their “Osteopetrosis and Dense Bone Dysplasia Panel Plus.” Sequence and copy number variation analysis did not examine LRP6, but instead LRP5 as well as AMER1, ANKH, CA2, CLCN7, COL1A1, CTSK, DLX3, FAM20C, CJA1, LEMD3, OSTM1, PT DDS1, PTH1R, SLC29A3, SLC2A1, SNX10, SORT, TCIRG1, TGFBI, TNFRSF11A, TNFRSF11B, TNFRSF11, and TYROBP. No mutation was identified. Therefore, in our laboratory, following informed written consent approved by the Human Research Protection Office,
Washington University School of Medicine, St. Louis, MO, USA, we amplified by PCR and Sanger-sequenced exclusively LRP6 exons 2–4 encoding the LRP6 first β-propeller. We designed the primers (12) (available upon request). Subsequently, DNA from each family member was Sanger-sequenced, blinded to their clinical information, selectively for the proposita’s LRP6 missense mutation (see Results).

Genes involved further in the WNT/β-catenin pathway were not assessed.

Statistical analyses

Height Z-scores were calculated using the SAS program of the US Centers for Disease Control and Prevention (CDC) growth chart website (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm) for sex-matched individuals 0 to 20 years of age. For the proposita and her sister, reference information was based on the data from the 20-year-old control women. Regression analysis was chosen to explore if LRP6 HBM spine, total hip, or femoral neck aBMD (g/cm²) was associated with age. Subsequently, we also considered: (i) aBMD data added from our two previous reports of LRP6 HBM (12,13) and then separately (ii) our experience (12) and other relevant publications (14–22) concerning aBMD in LRP5 HBM. Statistical analyses and graphics utilized SAS software 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided p < 0.05 was deemed statistically significant.

Results

LRP6 mutation analysis

Sanger sequencing selectively of the proposita’s LRP6 exons 2–4 showed in exon 4 a unique heterozygous missense variant (c.719C>T, p.Thr240Ile). This variant is not reported in the gnomAD browser as of October 2022. Likewise, none of the three previously published LRP6 HBM mutations are reported in gnomAD. Using PolyPhen2 (Polymorphism Phenotyping v2), this new variant is predicted to be “probably damaging” with a score of 0.968 (sensitivity: 0.77; specificity: 0.95). Using the sorting intolerant from tolerant (SIFT) algorithm, this variant is predicted...
Family findings

The family’s key demographic, clinical, DXA, and biochemical findings, discussed below, are summarized in Table 1.

Clinical phenotype

The family considered themselves healthy. One unaffected (II-2) and two affected (I-1, II-3) family members had suffered a single upper-limb fracture during childhood. None considered swimming difficult. Routine clinical examination as well as evaluation of photographs of the teeth and hard palate revealed torus palatinus in the two affected women (I-1, I-2) and in an early form in the affected 16-year-old son (II-4), but not in the two youngest affected sons (II-3, II-5) (Fig. 3) or in their unaffected siblings (II-1, II-2). There was no congenital hypodontia, exostoses surrounding teeth, or other noteworthy dental findings. Three of the five affected individuals (I-2, II-4, II-5), but neither of those unaffected (II-1, II-2), were tall (ie, >97th centile), consistent with our experience concerning both LRP5 and LRP6 HBM (Table 1).12

DXA findings

Elevated lumbar spine, total hip, and femoral neck aBMD Z-scores were found exclusively in all five family members harboring the LRP6 mutation. The tall stature of the three affected sons (I-2, II-4, II-5) perhaps artifactualy increased, but slightly, their aBMD (g/cm²) values. The aBMD Z-scores of the proposita and her sister averaged nearly +8 in the lumbar spine and +6 in the total hip (Table 1).

Linear regression analysis indicated the aBMD Z-scores individually for the lumbar spine and total hip, but not in the femoral neck, increased approximately +2 SD from childhood to middle age. This finding was then supported by regression analysis using the mean values of the combined Z-scores of these three skeletal sites versus age (Fig. 6). Our prior observations12 for LRP6 HBM suggested a significant positive association of increasing aBMD Z-scores in the lumbar spine but not total hip and for LRP5 HBM no such association.12 Now, pooling all of our LRP6 HBM data12,13 and separately published data12,14–22 concerning LRP5 HBM, supported such associations with increasing age (Supplemental Appendix S1).

Biochemical findings

Mineral homeostasis of all family members was normal, including normal serum calcium and phosphorus levels. Parathyroid hormone, measured only in the proposita, was normal. In those individuals with LRP6 HBM, serum alkaline phosphatase and pro-collagen type 1 N-terminal peptide levels were age-appropriate despite their sourcing from elevated skeletal mass (Table 1).

Discussion

Below, we briefly review the discovery, nosology, genetic basis, and pathogenesis of LRP5 HBM and LRP6 HBM and then consider their phenotypic similarities and differences.

Discovery, nosology, and etiology

What we now call HBM has been described in the medical literature for at least one-half century, but its expanding taxonomy has impeded recognition and understanding. In 1966, HM Worth and DJ Wollin28 suggested hyperostosis corticalis generalisata congenita for this autosomal dominant disorder, aiming to distinguish it from autosomal recessive van Buchem disease (hyperostosis corticalis generalisata familiaris).29 Subsequently, the term “Worth-type endosteal hyperostosis,” correctly emphasizing the radiographic hallmark of endosteal bone thickening, became widely adopted.30,31 However, starting in 1986, some reports used the designation “autosomal dominant osteopetrosis, type 1” (ADO1).32 Although osteoclast failure is not the principal pathogenetic feature, yet this term persists (OMIM # 607634).30 We have endorsed12,31 “HBM,” coined by Johnson and colleagues33 in 1997 when they linked the LRP5 HBM phenotype to chromosome 11, but recognize that LRP6 HBM must now be distinguished from LRP5 HBM. In 2022, Bergen and colleagues34 proposed an ontology based upon the biological process and/or pathway for monogenic
Table 1. LRP6, Demographic, Clinical, DXA, and Biochemical Findings of Family Members

<table>
<thead>
<tr>
<th>Subject</th>
<th>LRP6 mutation</th>
<th>Age/sex</th>
<th>Height (cm, percentile, Z-score)</th>
<th>Fractures</th>
<th>Hearing/eyes</th>
<th>Torus</th>
<th>Other</th>
<th>Spine Z-score</th>
<th>Total hip Z-score</th>
<th>Femur neck Z-score</th>
<th>L₁, L₄ aBMD (g/cm²)</th>
<th>Calcium (corrected)mmol/L</th>
<th>Phosphate mmol/L</th>
<th>ALP U/L</th>
<th>P1NP μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>+</td>
<td>44 ♀</td>
<td>160 (40) (−0.25)</td>
<td></td>
<td>Normal</td>
<td>Yes</td>
<td>Cervical stenosis; headaches</td>
<td>+7.7</td>
<td>+6.9</td>
<td>−5.5</td>
<td>2.107</td>
<td>2.37</td>
<td>1.29</td>
<td>82</td>
<td>39</td>
</tr>
<tr>
<td>II-1</td>
<td>−</td>
<td>15 ♂</td>
<td>163 (31) (−0.50)</td>
<td>No</td>
<td>Good</td>
<td>No</td>
<td>Dyslexia</td>
<td>+0.3</td>
<td>−0.1</td>
<td>−0.7</td>
<td>1.010</td>
<td>2.38</td>
<td>1.44</td>
<td>263</td>
<td>648</td>
</tr>
<tr>
<td>II-2</td>
<td>−</td>
<td>13 ♀</td>
<td>151 (17) (−0.95)</td>
<td>No</td>
<td>Good</td>
<td>No</td>
<td>Dyslexia</td>
<td>+1.8</td>
<td>+1.4</td>
<td>+1.9</td>
<td>1.112</td>
<td>2.38</td>
<td>1.82</td>
<td>260</td>
<td>611</td>
</tr>
<tr>
<td>II-3</td>
<td>+</td>
<td>10 ♂</td>
<td>131 (14) (−1.1)</td>
<td>[L] wrist age 6 years</td>
<td>Grommets age 6 years</td>
<td>No</td>
<td>Bifid uvula</td>
<td>+2.5</td>
<td>+4.7</td>
<td>+4.8</td>
<td>0.989</td>
<td>2.35</td>
<td>1.45</td>
<td>295</td>
<td>737</td>
</tr>
<tr>
<td>I-2</td>
<td>+</td>
<td>41 ♀</td>
<td>176 (98) (2.05)</td>
<td>None</td>
<td>Good</td>
<td>Yes</td>
<td>Rheumatic fever as a child</td>
<td>+7.9</td>
<td>+5.4</td>
<td>+4.2</td>
<td>2.126</td>
<td>2.33</td>
<td>1.33</td>
<td>60</td>
<td>38</td>
</tr>
<tr>
<td>II-4</td>
<td>+</td>
<td>16 ♂</td>
<td>193 (&gt;97) (1.88)</td>
<td>None</td>
<td>Keratoconus age 15 years</td>
<td>Early</td>
<td></td>
<td>+5.4</td>
<td>+4.8</td>
<td>+5.8</td>
<td>1.866</td>
<td>2.40</td>
<td>1.33</td>
<td>101</td>
<td>326</td>
</tr>
<tr>
<td>II-5</td>
<td>+</td>
<td>7 ♂</td>
<td>140 (&gt;97) (1.88)</td>
<td>None</td>
<td>Normal</td>
<td>No</td>
<td></td>
<td>+5.8</td>
<td>+3.8</td>
<td>+4.2</td>
<td>1.143</td>
<td>2.35</td>
<td>1.52</td>
<td>208</td>
<td>709</td>
</tr>
</tbody>
</table>

*aYellow shaded area reports the two family members without the LRP6 mutation.
*bSerum calcium. Normal range: 2.15–2.55 mmol/L.
*cSerum phosphate. Normal ranges: 1.06–1.70 mmol/L, ages 5–15 years; 0.8–1.4 mmol/L, ages >15 years.
*dALP (alkaline phosphatase). Normal ranges: 80–500 U/L, ages 5–10 years; 60–450 U/L, ages 11–16 years; 40–130 U/L, adult.
*eP1NP (procollagen-1 N-propeptide). Normal ranges: 250–800 μg/L, ages 5–10 years; 380–1050 μg/L, ages 11–16 years; 20–80 μg/L, adult. Measured by electrochemiluminescence (E170, Roche Diagnostics, Mannheim, Germany).
disorders that feature elevated bone mass. Following uniform Gene Ontology terminology, LRP6 HBM would fit within the sub-group 24 that includes LRP5 HBM, sclerosteosis (types 1 and 2), van Buchem disease, craniodiaphyseal dysplasia, and several other heritable disorders that involve dysregulation of WNT signaling.\(^{(34)}\)

The genetic basis of LRP5 HBM was discovered by two groups.\(^{(14,17)}\) In two American kindreds in 2002, the identical heterozygous missense mutation was identified in LRP5 (c512G>T, p.Gly171Val). Initially, LRP5 HBM was considered “non-syndromic”\(^{(14)}\) by lacking signs, symptoms, or complications, although buoyancy was poor during swimming. In the second kindred\(^{(17)}\) the “syndromic” broad jaw and torus palatinus of affected individuals was emphasized. However, in 2004, we reported a young American woman carrying the identical LRP5 mutation\(^{(15)}\) but suffering cranial nerve palsies, Chiari I malformation, diffuse skeletal pain, and dental exostoses, thereby revealing that LRP5 HBM can be a dento-osseous disease. Several publications have further characterized LRP5 HBM\(^{(4,12,14–22,35,36)}\) and disclosed 16 causal heterozygous mutations that disrupt the first β-propeller of LRP5 (Fig. 7).\(^{(14–20,22,26,35–41)}\)

We discovered LRP6 HBM in 2019\(^{(12)}\) when evaluating two small American families with a disorder closely resembling LRP5 HBM but lacking an LRP5 mutation and perhaps adding

Fig. 6. Fit plots of areal bone mineral density (aBMD) Z-scores versus subject ages. All five family members with LRP6 high bone mass (HBM) have elevated aBMD Z-scores in their (A) lumbar spine, (B) total hip, and (C) femoral neck (green bar indicates ±2 SD control mean). These Z-scores in the lumbar spine and total hip, but not femoral neck, appear to increase with age. (D) Using the mean of each subject’s three site-specific Z-scores supports this correlation of increasing aBMD with age (\(p = 0.0366\)).
LRP5 and LRP6 HBM pathogenesis

HBM, van Buchem disease (OMIM # 239100) and sclerosteosis types 1 and 2 (OMIM #269500, #614305), all considered “endosteal hyperostoses,” have in common a pathogenesis that involves deficient inhibition of bone formation by sclerostin.\(^{3,4}\) LRP5 and LRP6 proteins are 70% identical and 83% homologous (excluding amino acids 1–30 of LRP5 and 1–18 of LRP6).\(^ {12}\) LRP5 and LRP6 are single-pass transmembrane proteins with multiple domains. They bind Wnt ligands as well as sclerostin and dickkopf1.\(^ {36–38}\) At their N-terminus, the first 24 amino acids of LRP5 and the first 19 of LRP6 are the signal peptide that enables them to cross the plasma membrane.\(^ {26,39}\) The extracellular portions include four tandem YWTD-type β-propeller domains, which precede an epidermal growth factor (EGF)-like domain, which precedes three LDLR type A domains. The YWTD positions and sequences are highly conserved, but less so the LDLR repeats essential for ligand binding. LRP5 and LRP6 couple related, but not necessarily highly similar, ligands,\(^ {42–45}\) including many Wnts (eg, Wnt1, Wnt2, Wnt7b, Wnt8a, Wnt9a, Wnt9b, and Wnt10b) that interact with the first β-propeller domain.

Three of the now four LRP6 HBM mutations affect amino acids that are also implicated in LRP5 HBM (Fig. 5). Two LRP6 missense mutations (c.602C>T, p.Ala201Val, and the one carried by the current family c.719C>T, p.Thr240Ile) are precisely homologous to mutations causing LRP5 HBM.\(^ {38,39}\) The third LRP6 missense mutation (c.553A>C, p.Asn185His) affects the homologous amino acid position, with a different amino acid change.\(^ {39}\) The fourth LRP6 defect (c.678T>Adel679-684, p.His226Gln-del227-228ProPhe) is adjacent to a homologous LRP5 mutation.\(^ {13}\)

Biallelic mutations affecting LRP5 elsewhere than its first β-propeller cause the autosomal recessive disorder called osteoporosis-pseudoglioma syndrome (OMIM # 259770)\(^ {30}\) featuring severe osteoporosis and blindness.\(^ {46}\) LRP6 is present in many tissues. Lrp6, but not Lrp5, null mice die at birth,\(^ {47}\) suggesting Lrp6 has the greater prenatal importance. Biallelic mutations of LRP6 in humans are presumably embryonically lethal, therefore yet to be reported.

Heterozygous LRP5 mutations, elsewhere than the first β-propeller, may cause low bone mass, sometimes ocular complications,\(^ {48}\) but also mesiodenothagensis, root malformation, and taurodontism.\(^ {49}\) Such heterozygous variants in LRP6, too, have been associated with early-onset osteoporosis, although less often than similar LRP5 variants.\(^ {50}\) LRP6 single-nucleotide polymorphisms have been linked with high or low aBMD.\(^ {51,52}\) Furthermore, heterozygous mutations of LRP6 elsewhere than its first β-propeller have been associated with: (i) tooth agenesis with “oligodontia” (OMIM # 616724),\(^ {50,53–55}\) and rarely (ii) neural tube defects.\(^ {56}\) Most of the 16 LRP6 mutations associated with oligodontia alter the second or third β-propellers, whereas most associated with neural tube defects cluster in the second β-propeller or the intracellular domain.\(^ {56}\) LRP6 mutations elsewhere than affecting the first β-propeller have also been associated with early-onset atherosclerosis.\(^ {57–59}\) Of interest, Pickering and colleagues\(^ {60}\) in 2021 reported a young woman with skeletal changes resembling Camurati-Engelmann disease (OMIM #131300),\(^ {50}\) who carried a novel LRP6 defect that would compromise the second β-propeller, and Puente and colleagues\(^ {51}\) in 2022 reported familial low bone mineral density associated with a mutation in the second propeller region. These LRP6-associated disorders did not seem present in the family with LRP6 HBM we studied herein.

**Legend**
- Signal peptide
- LDL receptor-like ligand binding domains
- YWTD repeat domains
- Transmembrane domain
- EGF-like domains
- Cytoplasmic domain

**Fig. 7.** LRP5 and LRP6 mutations causing high bone mass (HBM). LRP5/6 protein showing HBM mutations. LRP5 mutations are shown above the protein and LRP6 mutations are shown below. The legend shows LRP5/6 domains. Each series of YWTD repeat domains comprises a β-propeller.
Clinical comparison of LRP5 and LRP6 HBM

Reflecting the cognate co-receptor function of their encoded proteins, LRP5 and LRP6 HBM phenotypes are remarkably similar. In the family herein, the five individuals with LRP6 HBM considered themselves healthy, although some reported low-level bone pain or arthralgias, yet were “syndromic” with acquired broad jaws and torus palatinus. In LRP5 HBM, it seems the age when torus palatinus appears is uncertain. The LRP5 HBM literature concerns 20- to 77-year-old people, with torus reported in 19 of 24 (79%); the five without this exostosis were 23 to 76 years of age. Beals suggested that with age the torus “increases slowly in size,” but later commented that “the age when torus palatinus appears has not been documented.” Our findings suggest that the torus palatinus of LRP6 HBM begins in adolescence. It was uncertain if the proposita’s cervical disk prolapse and arthralgias were related to her LRP6 HBM. In each of our two prior reports of LRP6 HBM, one episode of transient facial nerve palsy had affected a child but was explained by trauma or infection. Persisting cranial nerve compression has not complicated LRP6 HBM, although MRI of the Argentine student showed subtle stenosis of the optic canals and narrow internal auditory canals. Above average height seems characteristic and similar in both LRP5 HBM and LRP6 HBM. Thus far, our impression is that exostoses that obscure especially the posterior teeth, absent on routine physical examination of the family herein, are less severe in LRP6 HBM compared with LRP5 HBM. Hypodontia (particularly congenital absence of the maxillary lateral incisors) has occurred in LRP6 HBM but not in LRP5 HBM. However, the family herein reveals that oligodontia, too, is not invariable in LRP6 HBM, and perhaps previous associations were coincidental because absence of adult maxillary lateral incisors is a prevalent autosomal dominant form of oligodontia.

Mineral homeostasis seems intact in LRP5 HBM and LRP6 HBM. Bone turnover markers are in the high-normal range, but perhaps this reflects their sourcing from elevated bone mass. In 2019, we reported the principal radiographic features of both LRP5 HBM and LRP6 HBM were: (i) generalized osteosclerosis, (ii) uniformly thickened diploic space in the skull (sometimes so dense there is no trabecular pattern), (iii) poor development (aeration) of the frontal and maxillary sinuses, (iv) radiodense orbital roofs and facial bones, (v) mandible with obtuse angle and rounded body, (vi) teeth obscured by exostoses, (vii) submental process protrusion, (viii) molar and premolar teeth, and (ix) diffusely sclerotic vascular bones. Bone turnover is increased by recent availability of monoclonal antibodies against sclerostin to treat low bone density. Now, LRP6 analysis should be considered for unexplained generalized elevation of bone density. Our experience indicates good health in LRP6 HBM, at least until middle age, but study of affected elderly will be especially significant because LRP action is multifaceted and important. In LRP6 HBM, the increasing aBMD Z-score in the lumbar spine during growth may be concerning or may plateau and be protective against age-related bone loss. The significance of understanding LRP6 HBM and LRP5 HBM has been increased by recent availability of monoclonal antibodies against sclerostin to treat low bone density, especially if given to children.

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Disclosure

The authors declare no conflicts of interest.

Author Contributions

All authors approved the submitted manuscript. MPW arranged for mutation analysis of LRP6, performed by SD and assessed by SM, and then developed this report. JCB described the radiological findings. HS interpreted the photographs of the family’s dentition. Biostatistician FZ helped identify the association of bone density with patient age. TC selected, evaluated, and summarized the testing that identified and characterized the family’s LRP6 HBM, and then reviewed background literature and data.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbm4.10717.

References


