

Case Report

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# Potential therapeutic response in a severe case of autosomal dominant osteopetrosis type I

Syed Maisam Jafri<sup>1</sup>, Elizabeth A. Burke<sup>1</sup>, David R. Adams<sup>1</sup>, Colleen Evans<sup>1</sup>, Dorothy Bulas<sup>1</sup>, Stuart A. Weinerman<sup>2</sup>, Kristen Pan<sup>3</sup>, Michael T. Collins<sup>3</sup>, Thomas C. Markello<sup>1</sup>, Gilbert Vezina<sup>1</sup>, William A. Gahl<sup>1,4</sup>, Camilo Toro<sup>1</sup>

<sup>1</sup>NIH Undiagnosed Diseases Program, Common Fund, Office of the Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA.

<sup>2</sup>Endocrinology at Great Neck, Northwell Health Physician Partners, Great Neck, NY 11021, USA.

<sup>3</sup>National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892, USA.

<sup>4</sup>Section on Human Biochemical Genetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA.

**Correspondence to:** Dr. Camilo Toro, NIH Undiagnosed Diseases Program, Common Fund, Office of the Director, National Human Genome Research Institute, National Institutes of Health, 10 Center Dr., Room 3-2251, Bethesda, MD 20892, USA. E-mail: toroc@mail.nih.gov

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## Abstract

The low-density lipoprotein receptor-related protein 5 gene (*LRP5*), which encodes a coreceptor within the canonical Wnt signaling pathway, plays a crucial role in bone mass regulation and has been associated with several bone disorders. Autosomal dominant osteopetrosis type I (ADO type I, OMIM 607634) is a rare disease caused by heterozygous, gain-of-function mutations in *LRP5*. Here we describe a 44-year-old female who presented with thickened calvarium, elevated bone density, torus palatinus, mandibular exostoses, enlarged mandible, and disabling headaches and bone pain. Exome sequencing revealed a previously reported heterozygous missense variant in the *LRP5* gene (p.A242T). Post-diagnosis cranial vault volume measurement by computed tomography 3D reconstruction demonstrated decreasing intracranial volume over time. Off-label use of leuprolide acetate was associated with apparent stabilization of skull mineralization. This report documents a severe example of ADO type I and provides anecdotal evidence of the utility of therapy in need of formal evaluation.



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**Keywords:** Lipoprotein receptor-related protein 5 gene (*LRP5*), osteopetrosis, high bone mass, whole-exome sequencing (WES), leuprolide acetate

## INTRODUCTION

The canonical Wnt signaling pathway is tightly regulated to maintain a balance between bone formation and resorption. The pathway is activated by the formation of a protein complex consisting of the secreted signaling protein Wnt, the Frizzled transmembrane receptor, and the co-receptor LDL receptor-related protein 5 (*LRP5*). The downstream signaling cascade produced by the complex inhibits proteosomal degradation of  $\beta$ -catenin.  $\beta$ -catenin subsequently accumulates in the cytoplasm and migrates to the nucleus, where it acts as a transcriptional co-activator to control Wnt target gene expression that promotes bone formation<sup>[1]</sup>. This signaling cascade is modulated by several protein families including the secreted inhibitors sclerostin (SOST) and Dkkopf (DKK1), which bind *LRP5* receptors to prevent the formation of the Wnt-receptor complex<sup>[2]</sup>.

As a critical regulator of bone formation, *LRP5* has been associated with several bone disorders. Mutations that inactivate the *LRP5* gene lead to low bone mass; homozygous mutations cause a severe early-onset osteoporosis disorder called osteoporosis-pseudoglioma syndrome (MIM 259770), whereas heterozygous carriers display a milder form of osteoporosis<sup>[3]</sup>. *LRP5*-activating or gain-of-function mutations cause high bone mass in Autosomal Dominant Osteopetrosis type I (ADO type I; MIM 607634)<sup>[4,5]</sup>. Causative variants for ADO type I cluster in the first  $\beta$ -propeller of the extracellular domain of *LRP5*, which is an important region for binding Wnt inhibitory proteins, DKK1 and SOST. The location of these variants prevents the action of these antagonists and allows for unopposed canonical Wnt signaling that leads to increased bone formation<sup>[6]</sup>.

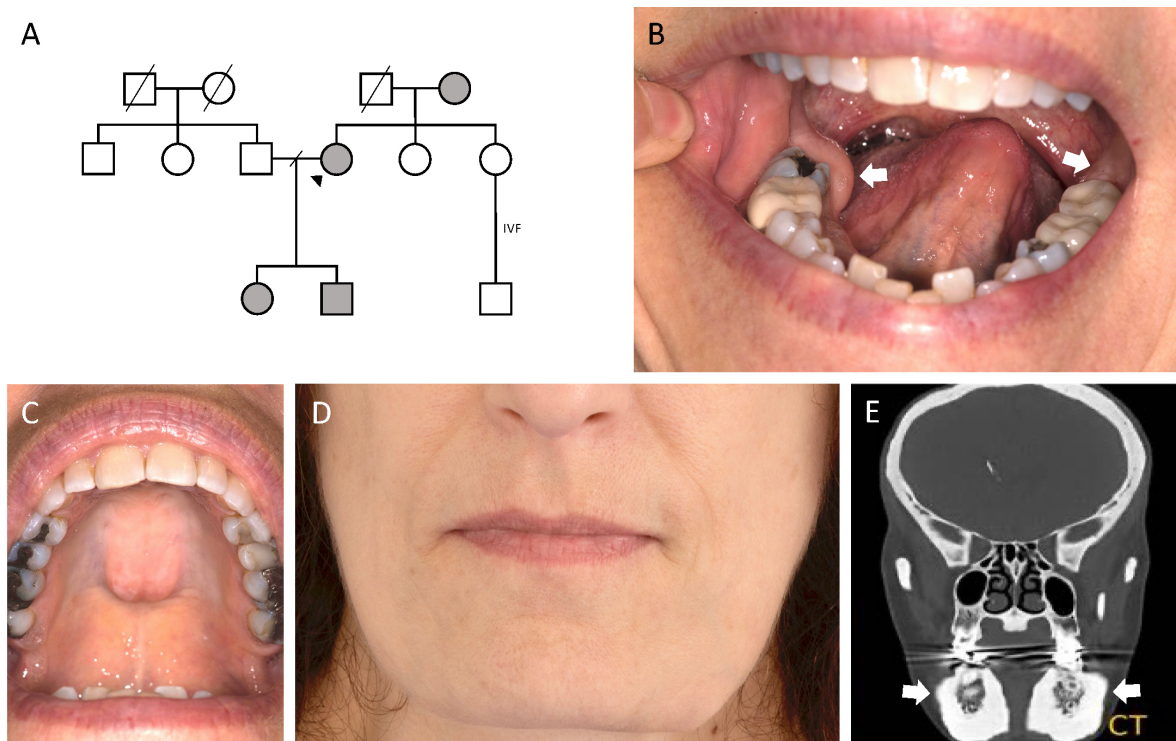
ADO type I features generalized osteosclerosis that is most notable in the cranial vault. In contrast to other types of osteopetrosis, ADO type I is not typically associated with fractures. The clinical presentation may include chronic bone pain, headaches and manifestations of cranial nerve impingement such as blurred vision. Other indicators of ADO type I are the presence of torus palatinus, enlarged mandible, and negative buoyancy<sup>[7-9]</sup>.

Here we describe the detailed clinical course of a 44-year-old woman who was referred to the National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP)<sup>[10]</sup> to identify a cause for her severely elevated bone density. Clinical exome sequencing revealed a heterozygous missense mutation in *LRP5*. The specific mutation has been reported previously in the context of osteopetrosis and therefore constituted strong evidence for a diagnosis of ADO type I. Our case is notable for its severity, progression and potential response to therapy, which provides insight into possible contributing factors and therapeutic options for patients with ADO type I.

## CASE REPORT

### Clinical report

The study participant is a 44-year-old woman with Russian Jewish (paternal) and Polish/Ashkenazi Jewish (maternal) ancestry [Figure 1A]. She reported frequent migrainous headaches and an inability to float in water present from a young age. At age 24 years, hip and joint pain were noted following the delivery of her first child [Supplementary Figure 1]. Her pain worsened over time. At approximately 28 years of age, she gave birth to her second child and noticed changes in the shape of her skull, including thickening of her forehead and the inside of her mouth and jaw. At age 32, she began experiencing chronic bone pain and



**Figure 1.** Pedigree and clinical findings. (A): Family pedigree illustrates the autosomal dominant inheritance pattern of ADO type I. Physical features noted during evaluation include; (B): crowded lower front teeth and bilateral bony protrusions posterior to the second molars (arrows); (C): torus palatinus; (D): square-shaped and enlarged mandible; and (E): thickening of the mandible (arrows) and calvarium demonstrated by coronal CT image. CT: Computed tomography.

frequent headaches. She was found to have thickening of her mandible and calvarium, but no abnormality in the long bones. Her bone density, at age 34, was elevated with a lumbar spine Z-score of +7.3 and a total hip Z-score of +8.0. By 36 years of age, her pain and symptoms had continued to increase in severity, and she developed episodic dizziness. She was hospitalized for evaluation after reporting sudden and severe occipital pain. Magnetic resonance imaging and computed tomography (CT) scans of the head revealed hydrocephalus and cerebellar tonsillar descent with crowding of the space directly above the foramen magnum. The cerebellar findings were attributed to decreasing volume of the posterior fossa due to skull thickening. A ventriculoperitoneal (VP) shunt was placed to relieve pressure on the brain. Her dizziness and occipital pain resolved following the VP shunt placement and migraine frequency dropped significantly.

At 41 years of age, she noted increasing back pain and was found to have disk herniations. Treatment included a triple disectomy with fusion of her cervical spine (C4-C7). During the procedure, her bones were noted to have a hard consistency, to the point of causing breakage of surgical equipment.

Anastrozole and leuprolide acetate, two therapeutics known to have side effects of decreasing bone mineral density through their effects on sex hormone levels, were trialed in an empiric, off-label manner. The patient was placed on anastrozole at age 42 for six months with no discernable results. She started leuprolide acetate (injection every three months) at age 42.6, which caused a mild decrease in symptoms and bone density and seemed to have a stabilizing effect on her bone disease. It was discontinued at age 46.7 due to the expense. Around the time of these treatments, there was an episode of acute chest pain and a new diagnosis of pericarditis, which resolved without intervention. In addition, there was one episode of

abdominal pain that resolved with VP shunt replacement.

The continuing bone evaluation included an iliac crest bone biopsy. The cortex was found to be markedly thickened, with a cortical width more than twice the upper limit of the reference range. Dense lamellar bone and cortical porosity appeared to be reduced. Osteons were found to be quiescent, while osteoblast and osteoclast morphology was normal. Osteons with active osteoclasts and eroded surfaces were occasionally seen. Cancellous bone, adjacent to endocortical surface, exhibited thickened trabeculae with normal lamellar structure. Residual calcified cartilage was not found.

At the age of 44, the patient was evaluated for the first time at the NIH. Her height was at the 5th centile, while head circumference was at the 98th centile. Hand and palm lengths were at the 1st and < 1st centiles, respectively. Physical examination was notable for bilateral bony protrusions posterior to the second molars that caused crowding of the lower front teeth [Figure 1B]. The presence of torus palatinus, a non-specific but characteristic sign of osteopetrosis, was also noted [Figure 1C]. The mandible was square-shaped and enlarged [Figure 1D-E]. The calvarium was thickened [Figure 1E]. Palpable ridges were appreciable on her forehead. The patient had essentially normal hearing for speech and pure tones bilaterally except for mild high-frequency hearing loss confined to 6000-8000 Hz in the left ear. She reported constant dull pain with intermittent bouts of shooting pains, in addition to less intense systemic bone pain. Even though the patient had trouble staying asleep and reported waking up 15-20 times in the night, she had no difficulty falling asleep. She denied psychological problems and reduced her pain with non-steroidal anti-inflammatory drugs. At a follow-up evaluation, she reported that she had a lumbar 4-5 spinal fusion performed at the age of 51 years.

At the time of the patient's first evaluation at the NIH, her 20-year-old son was discovered to have the beginning of a torus palatinus and increased bone density with Z-scores of +3.7 at the hip and +3.8 at the spine. Her 16-year-old daughter's Z-scores were also elevated at +5.3 at the hip and +4.5 at the spine despite having no other symptoms of ADO type I. The proband's mother also reported some bony growth on her upper and lower gums, a square jaw, and was determined to have high bone density with DXA Z-scores of +4.3 at the hip and +5.5 at the spine at the age of 65.

### Genetic analysis

Exome sequencing was conducted on the proband, her two children, two sisters, husband, and mother. The presence of the heterozygous missense NM\_002335.2: c.724G>A (p.A242T) variant in the fourth exon of the *LRP5* gene was revealed. Both of the proband's children and her mother were also found to have the same *LRP5* mutation and are affected by the disorder confirming an autosomal dominant mode of inheritance [Figure 1A]. This variant has been previously reported in several individuals in association with ADO type I<sup>[8,11,12]</sup>, and is not present in GnomAD v2.1.1<sup>[13]</sup>.

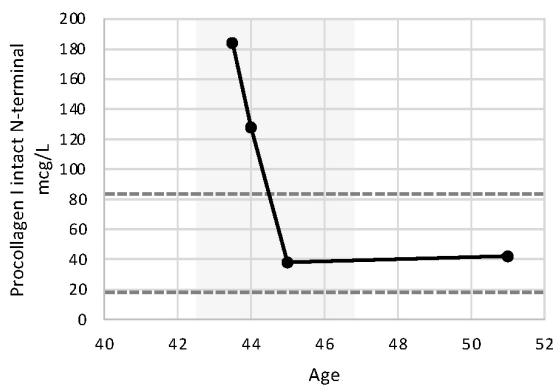
### Biochemical analysis

Markers of bone formation and bone resorption were serially measured in the patient's serum and urine [Figure 2A]. Notably, the two markers of bone formation, procollagen I intact N-terminal and bone-specific alkaline phosphatase, were elevated above normal ranges and subsequently reduced during leuprolide acetate treatment (indicated by gray color) [Figure 2A-C]. The markers of bone resorption, NTX-telopeptide and beta-C-terminal telopeptide ( $\beta$ -Ctx), consistently remained within normal ranges [Figure 2A].

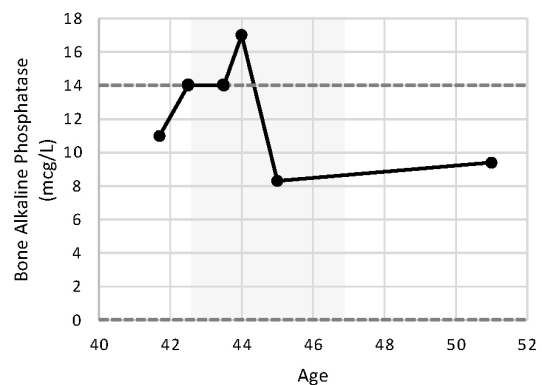
A

Analyte	Reference	Age 41.7	Age 42.5	Age 43.5	Age 44*	Age 45.8*	Age 51*
Urine NTX-Telopeptide	19-63 nM BCE/mM Cr	17	61	62	45	21	n/a
Procollagen I Intact N-terminal	preM 19-83mcg/L postM 16-96mcg/L	n/a	n/a	184 (H)	128 (H)	38	42
Bone Alkaline Phosphatase	preM <14mcg/L postM <22mcg/L	11	14 (H)	14 (H)	17 (H)	8.3	9.4
Beta-C-Terminal Telopeptide (B-Ctx)	preM 25-573 pg/mL postM 104-1008 pg/mL	n/a	n/a	n/a	553	427	386

B



C



**Figure 2.** Serial measurement of bone metabolism markers. (A-C) Markers were measured in serum or urine through the patient’s provider or the UDP (indicated by \*). Pre-menopausal (preM) and post-menopausal (postM) reference ranges are provided and values above the reference range are indicated by (H). Measurements made during the time of leuprolide acetate are shown in gray. (B-C) The region between the two dotted lines reflects the reference range for the patient’s age. UDP: Undiagnosed Diseases Program.

**Bone studies**

Bone densitometry (DXA) studies determined that the patient’s bone mineral density (BMD) was consistently high during her three visits to the NIH at ages 44, 45.8, and 51 [Table 1]. DXA Z-scores appear to stabilize during the period of leuprolide acetate treatment (in gray).

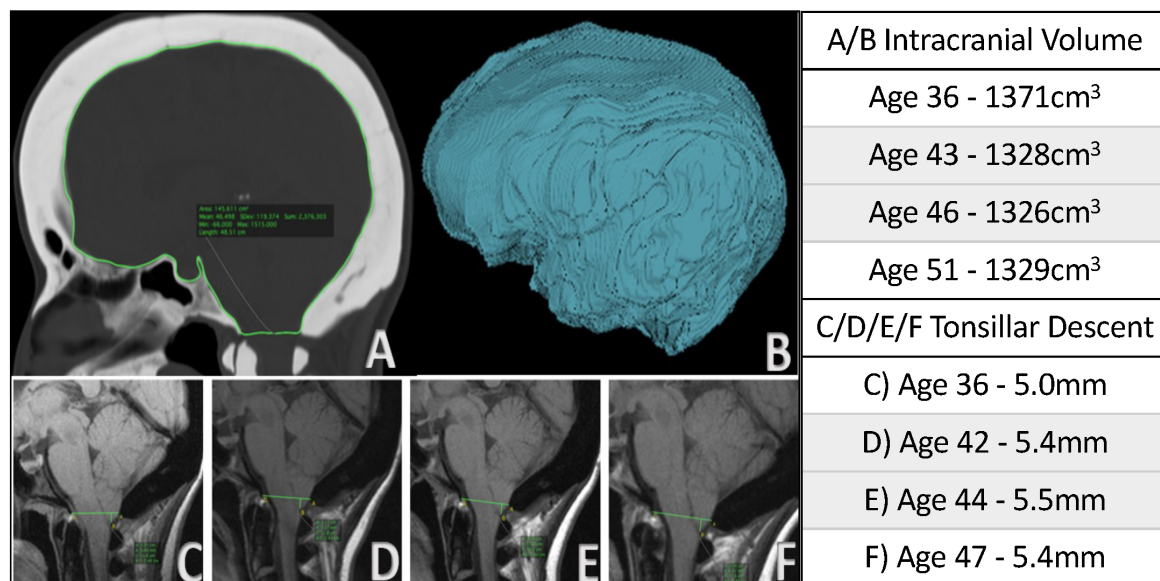
The patient’s CT scan showed diffuse osteosclerosis of the skull, cervical spine, and facial bones with thickening of the calvarium, skull base, and inferior mandible. Areas of increased sclerosis were observed along the sacroiliac joints iliac crests in the pelvis. Lower extremity long bones exhibited cortical thickening with a relative widening of the mid-portions of the diaphysis of long bones.

Cranial bone volume analysis determined that the patient’s intracranial volume decreased between the serial CT scans taken at age 36 and 46. However, the rate of volume reduction slowed or stabilized during the period of leuprolide acetate treatment (in gray). The intracranial volume showed a slight increase by age 51 [Figure 3A-B]. Measurements of the tonsillar descent showed a similar pattern of stabilization during treatment [Figure 3C-F].

**Table 1. Bone densitometry Z-scores**

Age	Lumbar spine Z-score	Total hip Z-score
34	7.3	8.0
39	6.5	5.8
<b>44*</b>	<b>6.0</b>	<b>5.8</b>
<b>45</b>	<b>5.9</b>	<b>5.0</b>
<b>45.8*</b>	<b>5.9</b>	<b>5.0</b>
48	6.2	4.8
51*	6.9	5.2

Serial DXA scans were performed by both the patient's provider as well as the UDP (indicated by \*). The scores measured during the time of leuprolide acetate treatment are shown in gray. UDP: Undiagnosed Diseases Program.



**Figure 3.** Cranial volume and tonsillar descent measurements. (A-B) Intracranial bone volume was measured by CT scan-based 3D reconstruction. (A) The software outlined the patient's intracranial space in 5 to 10 slices of each CT scan. (B) The software calculates volume using the outlined area and slice thickness. (C-F) Serial CT scans were used to measure the descent of the cerebellar tonsil. (A-F) Measurements performed on CT scans taken during leuprolide acetate treatment are shown in gray. CT: Computed tomography.

## DISCUSSION

Mutations in *LRP5* have previously been reported to cause the rare osteopetrosis disorder ADO type I. The symptomatic manifestations of elevated bone mass vary among affected individuals, but may include chronic bone pain, headaches, blurry vision, enlarged mandible, torus palatinus, resistance to bone fractures, and negative buoyancy<sup>[7,8]</sup>. Affected individuals are often unaware of the elevated density of their bones until revealed by an incidental radiology study.

Here we present a patient with a severe form of ADO type I, including a thickened calvarium with intracranial volume restriction and an anecdotal response to off-label therapy. The previously-described causative mutation is located in the fourth exon of the *LRP5* gene and affects the first  $\beta$ -propeller domain, a region important for binding inhibitory proteins. Protein modeling performed by Gregson *et al.* suggested that the degree of protein structure alteration and the resulting effect on SOST-LRP5 binding correlates

directly with the severity of the ADO type I phenotype<sup>[8]</sup>. The p.A242T mutation identified in our patient is predicted by computational model to alter the packing of the *LRP5* structure and destabilize the SOST binding site<sup>[8]</sup>. Another ADO type I associated variant, p.N198S, is predicted to directly disrupt the SOST binding site. These two variants are associated with a severe ADO type I disease course<sup>[8]</sup>. Reflecting the structural impact of these mutations, the p.N198S mutation has resulted in severe bone phenotypes with a BMD Z-score range from +5.6 to +12.2, while the p.A242T has been reported to cause a range of BMD Z-scores from +3.1 to +10.7<sup>[8]</sup>. Although the variant's impact on the protein appears to predict how high BMD scores can reach, there is considerable variability among patients with the same variant, suggesting that other factors may play a role in determining the severity of a patient's disease.

The patient's clinical course is of interest in that worsening symptoms seem to coincide with her pregnancies, indicating that sex hormones may influence the disease's progression. The onset of her bone pain and subsequent symptoms coincided with pregnancy and the delivery of her first child. A change in her skull shape, frontal bossing and an enlarged mandible were noted around the delivery of her second child. Progesterone and estrogen, sex hormones necessary for maintaining pregnancy, rise as pregnancy progresses. Estrogen is a well-known regulator of bone metabolism that directly interacts with bone cells to decrease bone remodeling and resorption as well as maintain bone formation<sup>[14]</sup>. Progesterone acts directly on cell surface receptors to increase bone production as well<sup>[15,16]</sup>. We posit that the increased estrogen and/or progesterone levels from the proband's two pregnancies may have exacerbated the *LRP5*-associated increase in bone mass. Although we were unable to collect data following the onset of menopause, a previous study suggested menopausal hormonal changes may also affect bone metabolism. Balemans *et al.* reported a female ADO type I patient who showed a 5% reduction in bone densitometry values between the ages of 50 and 55 after passing through menopause at 52<sup>[17]</sup>. While additional studies are needed to assess the true impact of sex hormone changes on ADO type I bone mass growth, this may be an important factor to consider with patients as it pertains to the management of their disease.

Currently, there are no recommended treatment options beyond pain management for ADO type I patients. In an effort to identify an effective therapy for this patient, leuprolide acetate and anastrozole were trialed in an empiric, off-label fashion. Leuprolide acetate is a synthetic gonadotropin-releasing hormone or luteinizing hormone-releasing hormone (GnRH or LH-RH) analog indicated for treating anemia, precocious puberty, endometriosis, and advanced prostate cancer. It has a known side effect of decreasing bone mineral density by suppressing the production of sex hormones<sup>[18]</sup>. Anastrozole is a nonsteroidal aromatase inhibitor used in the treatment of breast cancer, which blocks the production of estrogen. It also has a side effect of causing decreased bone mineral density<sup>[19]</sup>. While anastrozole was ineffective, leuprolide acetate reportedly had a positive effect. The treatment period (age 42.6-46.7) coincided with an improvement of symptoms, a mild decrease and stabilization of bone density scores, a normalization of bone formation marker levels, and an apparent change in the rate of intracranial volume loss suggesting stabilization of skull mineralization. Based on these observations, leuprolide acetate should be considered for a more rigorous evaluation of efficacy in the treatment of ADO type I.

In summary, we present a detailed clinical description of a patient with a severe presentation of ADO type I due to a heterozygous missense mutation in *LRP5*. Our results suggest that sex hormones may play an influential role in this disorder and should be considered when discussing disease management with patients. We also provide anecdotal evidence that leuprolide acetate may benefit patients with ADO type I. These observations raise the question of its utility for male or younger, asymptomatic patients with ADO type I and patients with other forms of osteopetrosis. Further studies are needed to evaluate all of these potential applications for leuprolide acetate and to identify new approaches to slow bone growth and

prevent the associated complications for those affected by this rare disease.

## DECLARATIONS

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### Authors' contributions

Provided clinical consult, summary, and interpretation: Adams DR, Colleen Evans, Evans C, Bulas D, Weinerman SA, Vezina G, Collins MT, Toro C

Collected and interpreted the data: Jafri SM, Burke EA, Evans C, Pan K, Collins MT, Markello TC

Wrote the manuscript: Jafri SM, Burke EA

Supervised the project: Adams DR, Collins MT, Gahl WA

All authors reviewed and revised the manuscript and approved the submission.

### Availability of data and materials

Not applicable.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

The study participant was evaluated by the UDP under the IRB approved protocol 76-HG-0238, "Diagnosis and Treatment of Patients with Inborn Errors of Metabolism or Other Genetic Disorders" (NCT00369421) following informed and written consent<sup>[20]</sup>.

### Consent for publication

A written informed consent for publication was obtained.

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