Journal of Research in
Orthopedic Science

February 2025. Volume 12. Number 1

Review Paper

Genetic Contributions to Bone Health and Disease: A Mini-review

Pouria Tabrizian[1], Morteza Nakhaei Amroodi[1], Khatere Mokhtari[2], Mohammadreza Bahaeddini[1], Mojtaba Baniasadi[1*]

1. Department of Orthopedics, Bone and Joint Reconstruction Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
2. Department of Cell and Molecular Biology and Microbiology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran.

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Citation Tabrizian P, Nakhaei Amroodi M, Mokhtari Kh, Bahaeddini M, Baniasadi M. Genetic Contributions to Bone Health and Disease: A Mini-review. Journal of Research in Orthopedic Science. 2025; 12(1):1-12. http://dx.doi.org/10.32598/JROSJ.12.1.2719.1

http://dx.doi.org/10.32598/JROSJ.12.1.2719.1

Article info:
Received: 04 Jul 2024
Revised: 13 Nov 2024
Accepted: 13 Dec 2024
Available Online: 01 Feb 2025

Keywords:
Bone health, Genetics, Bone mineral density (BMD), Metabolic bone diseases, Genetic mutations, Monogenic disorders, Polygenic traits

ABSTRACT

Bone health is a complex process governed by the interplay of genetic and environmental factors. This mini-review explores the contribution of genetic factors to bone health, with particular focus on their role in bone mineral density (BMD), osteoporosis, and metabolic bone diseases. BMD and fracture risk, which are influenced by genetics, exhibit high heritability, with estimates ranging from 50% to 85%. Significant genetic effects have been observed, particularly in the axial skeleton. Furthermore, genetic factors impact metabolic bone diseases, which can be monogenic or polygenic. Monogenic disorders, such as osteogenesis imperfecta, are linked to mutations in specific genes, while polygenic disorders involve multiple genetic variations that interact with environmental factors. The identification of genetic loci responsible for these conditions has provided insight into their molecular pathogenesis, offering potential therapeutic targets. Understanding genetic contributions to bone health is crucial for developing personalized treatment strategies for metabolic bone diseases.

*** Corresponding Author:**
Mojtaba Baniasadi, MD.
Address: *Department of Orthopedics, Bone and Joint Reconstruction Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.*
E-mail: *mojtaba.baniasadi20@gmail.com*

Introduction

Bone is a critical organ responsible for providing structural support to the body and maintaining mineral metabolism. It primarily comprises two main components: The bone matrix and bone cells. The bone matrix, which accounts for approximately 90% of the bone's volume, is divided into inorganic and organic components. The inorganic matrix is predominantly composed of calcium hydroxyapatite, while the organic matrix primarily consists of type I collagen, along with glycoproteins, growth factors, and proteoglycans [1-4].

Hereditary metabolic bone disorders are among the most varied groups of rare diseases. These conditions result from genetic disruptions in skeletal homeostasis, which may or may not involve changes in the circulating levels of calcium, phosphate, vitamin D metabolites, or other biomarkers. In recent years, advancements in molecular genetics and basic research have led to the development of innovative treatments, many of which have demonstrated promising efficacy [4].

The pathogenic mechanism underlying these genetic disorders arises from the inability of the mutated gene to encode a functional protein properly. This condition results in either the production of an abnormal protein or an insufficient quantity of a normal protein. To date, more than 5000 conditions have been associated with single-gene mutations, with at least 500 affecting the bones and joints [5]. Skeletal disorders resulting from single-gene mutations can be classified into two primary categories: Those that indirectly affect the skeleton by influencing other tissues and those that primarily manifest within the skeleton. The first category includes conditions such as neurofibromatosis, Gaucher's disease, and alkaptonuria, where the skeletal involvement is secondary to broader systemic effects. The second category comprises genetic conditions that directly affect the skeleton, commonly known as skeletal dysplasia or constitutional bone disorders [6].

The role of genetics in osteoporosis

Studies involving twins and families indicate that genetic factors play a substantial role in determining bone mineral density (BMD) and other factors contributing to the risk of osteoporotic fractures [7-12]. Family-based research has revealed high heritability estimates for BMD, with the most pronounced effects observed in young adults [13, 14]. Several additional factors contributing to osteoporotic fracture risk also display a heritable component. These include femoral neck geometry, hip axis length, bone ultrasound characteristics, biochemical markers of bone turnover, body mass index (BMI), muscle strength, and reproductive milestones such as the timing of menarche and menopause [15-25]. The evidence regarding the impact of genetic factors on bone loss remains inconsistent [9, 10, 12, 26-28]. Despite these limitations, it is well-established that genetic factors play a crucial role in the pathogenesis of osteoporosis. Numerous population-based studies support this, indicating that a family history of fractures is a significant risk factor for fractures, with mechanisms partly independent of bone density [29]. Osteoporosis is a multifactorial disease, thought to arise from the interplay between environmental factors and several genetic influences [12, 13]. In rare cases, osteoporosis follows a clear Mendelian inheritance pattern, like osteogenesis imperfecta and osteoporosis, which are linked with disabling mutations in the aromatase and estrogen receptor genes [30-32]. There have also been reports of families where unusually high bone mass is inherited as an autosomal dominant trait, indicating the involvement of a single gene with a substantial impact [33]. However, the severity of osteogenesis imperfecta can vary significantly both within and between families, even with identical mutations in the collagen genes [12, 34].

Metabolic bone diseases

Metabolic bone diseases encompass a diverse group of skeletal disorders characterized by disruptions in bone cell function, bone matrix protein composition, or overall mineral balance [35, 36]. Many metabolic bone diseases have a genetic origin, which can involve a germline mutation in a single gene, a somatic mutation in a single gene, or multiple genetic variants [37, 38]. There is considerable overlap between the genes responsible for monogenic skeletal disorders and those implicated in polygenic bone phenotypes. Identifying these loci has enhanced our understanding of the molecular mechanisms underlying skeletal diseases and revealed potential new therapeutic targets [39-41].

Inheritance

Generally, monogenic diseases are inherited through one of six modes of inheritance. Autosomal dominant, e.g. familial hypocalciuric hypercalcaemia (FHH) results from mutations in the calcium-sensing receptor (CaSR). Also, signaling pathways contribute to many genetic disorders, including autosomal recessive, X-linked, autosomal dominant, and non-Mendelian patterns. For instance, in autosomal recessive disorders,

vitamin D-dependent rickets types 1 and 2 are caused by mutations in the *CYP27B1* and *VDR* genes, respectively. In X-linked recessive conditions, Dent's disease, associated with mutations in the *CLC-5* gene, and X-linked hypophosphatemic rickets, resulting from mutations in the *PHEX* gene, are prominent examples. Autosomal dominant disorders typically involve significant genetic effects on bone metabolism, while Y-linked disorders, such as azoospermia and oligospermia, are linked to mutations on the Y chromosome [42].

Additionally, non-Mendelian mitochondrial defects, such as hypoparathyroidism in Kearns-Sayre syndrome and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, are also important components of this pathway [43-48]. Monogenic metabolic bone diseases can also result from sporadic postzygotic mosaicism, as seen in conditions like McCune-Albright syndrome. In these cases, the genetic mutation occurs after fertilization, resulting in genetically distinct cell populations within the individual. This type of mosaicism can cause a variety of clinical manifestations, including bone, skin, and endocrine abnormalities, as seen in McCune-Albright syndrome, in which the mutation in the *GNAS* gene leads to dysregulated hormone signaling and abnormal bone formation [49]. Digenic inheritance has been identified in a family with hereditary hypophosphatemic rickets and hypercalciuria, in which individuals carry heterozygous mutations in both *SLC34A1* and *SLC34A3*. The combined mutations in these two genes contribute to the pathogenesis of hereditary hypophosphatemic rickets with hypercalciuria, a disorder characterized by impaired renal phosphate reabsorption, leading to phosphate wasting, low serum phosphate levels, and associated bone mineralization defects [42]. Osteoporosis is a major metabolic bone disorder that represents a complex polygenic trait. More than 200 genetic loci have been linked to this common condition, highlighting the involvement of multiple genes in its pathogenesis. These loci are associated with various factors influencing BMD, bone turnover, and skeletal architecture, and they interact with environmental factors such as diet, physical activity, and hormonal changes. The identification of these loci provides valuable insights into the genetic basis of osteoporosis and may lead to the development of personalized prevention and treatment strategies [50, 51]. However, most loci associated with osteoporosis have likely yet to be identified. Monogenic forms of osteoporosis are characterized by specific genetic mutations that lead to altered bone remodeling processes, resulting in a higher susceptibility to fractures and reduced bone mass [52, 53].

Genetic heterogeneity

Many phenotypically similar metabolic bone disorders arise from mutations in various genes. For example, in osteogenesis imperfecta (OI), 85%-90% of cases are due to mutations in the *COL1A1* and *COL1A2* genes [54-58]. Similarly, hypophosphatemic rickets can be caused by mutations in genes encoding phosphatonins, such as *FGF-23*. Genetic defects disrupt phosphate homeostasis, leading to impaired bone mineralization and the clinical manifestations of rickets [59-64]. Additionally, FHH, a disorder of extracellular calcium homeostasis, is known to comprise three types, each caused by germline loss-of-function mutations in distinct genes. The first type is associated with mutations in the *CaSR*. The second type results from mutations in the G-protein subunit-α11 (*Gα11*), while the third type is linked to mutations in the adaptor-related protein complex-2 σ-subunit (*AP2σ*). These mutations impair calcium regulation, leading to the characteristic features of FHH [65-67].

Mutations in a single gene can result in distinct skeletal phenotypes [68-70]. In certain metabolic bone diseases, the severity of the condition can be influenced by the allele dosage and by whether the mutation is heterozygous or homozygous [70, 71].

Neurofibromatosis

Neurofibromatosis type 1 (NF1) is a genetic disorder caused by a mutation in the *NF1* gene, which encodes a tumor suppressor protein called neurofibromin. This condition is characterized by the development of cutaneous neurofibromas (benign skin tumors), café-au-lait spots (light brown skin patches), and plexiform neurofibromas (tumors along nerve trunks). Other common features include macrocephaly (an unusually large head), local gigantism, and an increased risk of central nervous system neoplasms (tumors in the brain or spinal cord). Skeletal changes are also common in many individuals with NF1, including scoliosis, tibial dysplasia, and other bone abnormalities. NF1 is one of the most common single-gene disorders, with an estimated 100000 individuals affected in the United States alone. The condition exhibits variable expressivity, meaning that the severity and range of symptoms can differ widely between individuals [72]. NF1 is typically diagnosed in infancy or childhood, with symptoms that progressively worsen as the patient ages. Although the skeleton is not the primary target of NF1, 30%-60% of individuals with NF1 are estimated to experience osseous abnormalities. These skeletal changes can include scoliosis, dysplastic changes in the tibia (often leading to an increased risk of fractures),

and other bone deformities. The skeletal manifestations of NF1 may be subtle at first but can become more pronounced over time, potentially leading to significant mobility and structural issues. The bone abnormalities in NF1 are thought to result from abnormal regulation of bone growth, which may involve the mutated *NF1* gene influencing the bone microenvironment and signaling pathways critical for normal bone development [73]. Scoliosis in NF1 is often progressive, and its development is believed to be linked to abnormal bone growth and the effects of the *NF1* gene on skeletal development [74]. Most cases of scoliosis in NF1 are attributed to osseous abnormalities in the vertebrae, including vertebral body wedging or scalloping. Alongside scoliosis, another orthopedic condition found in 13% of NF1 patients is congenital bowing and pseudarthrosis, particularly of the tibia [75, 76].

Gaucher disease

The skeletal manifestations of Gaucher disease include bone pain, fractures, osteopenia, osteoporosis, and characteristic radiologic features such as the Erlenmeyer flask deformity. Bone pain often results from the infiltration of Gaucher cells into the bone marrow, leading to increased pressure and inflammation within the bones. This condition can also lead to an increased frequency of fractures due to the compromised structural integrity of the affected bones. Osteopenia and osteoporosis are common because the disease disrupts normal bone remodeling, reducing bone density and strength. The Erlenmeyer flask deformity is a hallmark radiologic sign of Gaucher disease, seen in the long bones, particularly the femur and humerus. This deformity is characterized by widening of the metaphysis, resulting in a flask-like appearance. This radiologic finding is due to the accumulation of Gaucher cells in the bone marrow, causing altered bone growth and remodeling. In addition to these skeletal issues, patients with Gaucher disease may also experience progressive joint involvement, leading to pain and limited mobility. Osteonecrosis, particularly of the femoral head, is another complication that may arise, contributing to functional impairment. The severity and presentation of skeletal manifestations can vary widely depending on the Gaucher disease subtype (type 1, type 2, or type 3) and age of onset. Type 1 Gaucher disease, which is the most common and non-neuronopathic form, often presents with significant skeletal involvement but less severe neurologic complications compared to the other types. Management of the skeletal complications of Gaucher disease typically includes enzyme replacement therapy (ERT), which aims to reduce the accumulation of Gaucher cells in the bone marrow and other affected organs, and may help alleviate bone pain and improve BMD. In some cases, patients may require orthopedic interventions to address fractures or deformities. The development of novel therapeutic approaches, including gene therapy and substrate reduction therapy, holds promise for better management of the disease and its skeletal manifestations in the future [77-81].

Alkaptonuria (ochronosis)

Alkaptonuria, or ochronosis, is a genetic condition that indirectly affects the skeletal system. It is marked by the presence of dark urine and, in later stages, severe arthropathy accompanied by the deposition of darkly pigmented cartilage. This condition results from a deficiency in an enzyme that disrupts the breakdown of homogentisic acid, a byproduct of tyrosine and phenylalanine metabolism. The genetic mutation, located at an unidentified locus, leads to a deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid in tissues, which is then excreted in the urine [82]. Alkaptonuria can often be diagnosed shortly after birth because of the black discoloration of urine in diapers [79, 83]. Orthopedic issues generally manifest in early adulthood and are the primary cause of the most debilitating symptoms of the disease [84, 85]. The spine is usually the first area to exhibit signs of pigment deposition, affecting the intervertebral discs and paravertebral soft tissues. Patients often present with low back pain, stiffness, and nerve root compression [86]. The intervertebral disk spaces are typically reduced in width and often exhibit signs of calcification [87]. Involvement of large joints, such as the hips and knees, typically occurs later than spinal involvement. The articular cartilage in these joints becomes heavily stained with dark brown or black ochronotic pigment, giving it a distinct dark appearance [79, 88, 89]. While severe arthropathy in peripheral joints can often be effectively managed with total joint arthroplasty, spinal involvement tends to cause significant disability, often requiring patients to undergo prolonged periods of bed rest.

Genetic disorders with direct impact on the skeleton

Skeletal dysplasia, also known as constitutional bone disorders, is a group of conditions caused by single-gene mutations that primarily or solely affect the skeleton. Individuals with these disorders typically have short stature, and many also exhibit abnormally shaped bones. In some types of dysplasia, bones may be fragile. Although short stature itself normally does not lead to health problems, patients with skeletal dysplasia often experience

orthopedic disabilities that necessitate continuous medical care [90]. Orthopedists are responsible for managing complications related to skeletal fragility, as well as treating arthropathies and nerve impingements caused by abnormally shaped bones [91, 92]. The Nosology and Classification of Skeletal Disorders system includes 372 conditions, 215 of which are associated with one or more of 140 distinct genes [93]. Osteogenesis imperfecta is one of the most prevalent genetic skeletal disorders, impacting approximately 15000 to 20000 individuals in the United States. It is caused by mutations in one of the two COL1A genes that encode type 1 collagen. These mutations lead to fragile bones, osteopenia, and varying levels of skeletal deformities [79, 94, 95]. Since 1978, clinicians have commonly used the Sillence classification, which divides patients with osteogenesis imperfecta into one of four major phenotypes [96, 97]. Type I osteogenesis imperfecta follows an autosomal dominant inheritance pattern; however, approximately 20%-30% of patients have no family history, indicating the presence of new mutations [78].

Osteopoikilosis

Osteopoikilosis is a hereditary bone disorder characterized by increased bone density and is typically grouped with osteopetrosis syndromes. It follows an autosomal dominant inheritance pattern. While the molecular mechanisms underlying this condition remain poorly understood, it appears to result from localized disruptions in bone remodeling [98].

Achondroplasia

Achondroplasia is the most common skeletal dysplasia within the group of chondrodysplasias, which are disorders of cartilage growth and structure. It is a condition characterized by retarded cartilage growth, most notably at the growth plates. This delay in cartilage growth results in abnormally shaped, shortened bones —particularly long bones —due to a disruption in endochondral ossification. The disease is typically diagnosed at birth, and individuals with achondroplasia have markedly short stature by adulthood. Although achondroplasia is inherited as an autosomal dominant condition, 87% of cases arise from a new mutation, meaning affected individuals often have normal parents. The molecular cause of achondroplasia is a mutation in the gene that encodes FGFR3, located on the p16.3 locus of chromosome 4. The mutation results in a defective receptor that impairs cartilage growth, leading to the characteristic skeletal abnormalities observed in this condition [99]. In achondroplasia, a mutation in *FGFR3* enhances this negative feedback loop, severely inhibiting normal subchondral bone growth. This results in the characteristic skeletal abnormalities seen in achondroplasia, including short limbs and an overall short stature. The inhibition of endochondral ossification is the key pathophysiological feature of the disease [100]. In achondroplasia, the pathologic features are primarily due to a quantitative abnormality in cartilage growth and endochondral ossification, rather than a qualitative defect in cartilage itself. Early in development, bones are abnormally shaped, reflecting the disruption in the normal process of bone formation. The growth plate, which is essential for the lengthening of long bones, shows disorganization. The various zones of the growth plate—such as the resting, proliferative, and hypertrophic zones—are often abbreviated. This disorganization disrupts the orderly progression of cartilage maturation and ossification, preventing proper bone elongation. As a result, the cartilage cells do not proliferate and mature as they should, leading to shortened long bones and the characteristic features of achondroplasia, such as short stature and disproportionate limb length [101]. In achondroplasia, skeletal abnormalities are particularly evident in bones formed by endochondral ossification. The condition affects the epiphyseal plate, where transverse bars of bone, usually lamellar in structure, separate the epiphyseal plate from the metaphysis. This abnormal bone formation results in the characteristic short stature and limb deformities seen in the disorder. However, the articular cartilage remains normal, meaning that premature arthritis is not a typical feature of achondroplasia. Membranous bone formation, which affects the bones of the skull and clavicles, occurs normally in achondroplasia, so the width of the bones is unaffected. The radiographic features align with the clinical signs, with the skull being particularly affected. Patients often present with a large head (macrocephaly), prominent frontal bossing, and hypoplasia of the facial bones, particularly the nasal bridge. The base of the skull is underdeveloped due to abnormal cartilage growth, resulting in a small foramen magnum. This condition can cause spinal cord compression, which may contribute to hypotonia in infants with achondroplasia. The spine is also notably affected [102].

Pyknodysostosis

Pyknodysostosis, originating from the Greek term “punknos” meaning dense, is a rare autosomal recessive disorder marked by abnormally dense yet brittle bones, which lead to an increased tendency for fractures. The condition is caused by a homozygous mutation in exon 5 of the *CTSK* gene, which encodes cathepsin K, a lysosomal metalloproteinase vital for osteoclast-mediated

bone matrix breakdown [103]. The disorder involves decreased function of both osteoblasts and osteoclasts, leading to short-limbed dwarfism, distinctive facial deformities, increased bone density (osteosclerosis), bone fragility with recurrent fractures, and dental and nail abnormalities [103-105].

Juvenile Paget's disease

Juvenile Paget's disease, also known as osteitis deformans, is an uncommon hereditary condition marked by accelerated bone remodeling that typically appears in early childhood. The disorder is primarily linked to mutations in the *TNFRSF11B* gene, which encodes osteoprotegerin (OPG). It is most often inherited in an autosomal dominant manner, though the degree of expression can vary among individuals [106-108].

Paget's disease

Paget's disease is characterized by excessive bone turnover, resulting in disorganized bone remodeling. This condition leads to weakened bone structure, increased risk of fractures, and other skeletal abnormalities [109, 110]. It has been proposed that a slow virus could trigger Paget's disease. However, in 15%–40% of cases, the condition follows an autosomal dominant inheritance pattern, while the inheritance pattern in the remaining instances remains uncertain [111, 112]. The *SQSTM1* gene mutations are the primary genetic cause of Paget's disease. Research across different populations has shown that the p.P392L mutation is the most commonly observed, though other mutations have also been identified. These mutations usually impact the ubiquitin-associated domains of the SQSTM1 protein [113]. Other genes associated with the risk of Paget's disease include *TNFRSF11A*, which encodes the receptor activator of RANK, and *TNFRSF11B*, which encodes OPG [114-117].

Osteoarthritis

The genetics of osteoarthritis is complex, as it generally does not follow the classical Mendelian inheritance pattern and is likely influenced by interactions among multiple genes. A wealth of research supports the polygenic inheritance model, suggesting that osteoarthritis arises from the combined effects of various genetic factors rather than a single-gene defect. This polygenic nature reflects the multifactorial pathways involved in the disease, making its genetic basis more intricate and challenging to pinpoint [118, 119]. The onset, progression, and severity of the disease may be influenced by multiple genetic factors that interact with alterations caused by different genes. The genetic contribution to this disease is estimated to range from 35% to 65%. This figure suggests that genetic factors play a significant role in the development and severity of the disease, although they cannot fully explain all aspects of it. In fact, environmental factors and other physiological conditions may also contribute to the disease, further complicating the interactions between genetic and environmental influences [119]. Epidemiological studies suggest that the likelihood of inheriting osteoarthritis is approximately 40% for the knee, and 65% for the hands and hips. These estimates highlight a significant genetic contribution to the development of osteoarthritis in specific joints, with higher heritability observed in the hands and hips than in the knee. However, this also implies that other factors, such as environmental influences and mechanical stress, play an important role in the disease's onset and progression [119, 120].

Conclusion

Genetic factors play a critical role in regulating bone health, influencing BMD, fracture risk, and susceptibility to metabolic bone diseases. Advances in genetic research have improved our understanding of the molecular mechanisms underlying these conditions, identifying key genes involved in both monogenic and polygenic disorders. This knowledge not only enhances our understanding of bone pathophysiology but also opens the door to novel therapeutic approaches that modulate genetic pathways. Future research into gene-environment interactions and the development of targeted therapies will be pivotal in managing and preventing bone-related disorders.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization, supervision, project administration and funding acquisition: Mojtaba Baniasadi; Investigation: Khatere Mokhtari and Mohammadreza Bahaeddini; Writing the original draft : Pouria Tabrizian, Morteza Nakhaei Amroodi, and Khatere Mokhtari; Review and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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