GMR
The Original

GENETIC POLYMORPHISMS ASSOCIATED WITH OSTEOPOROSIS SUSCEPTIBILITY: A SYSTEMATIC REVIEW OF MOLECULAR VARIANTS AND BONE MINERAL DENSITY OUTCOMES

Mashael Saad Alotaibi[1], Abdulwahab Mufareh Hassan Assiri[2], Abdulelah Adnan Ahmed Alshebly[3], Abdulrahman Ahmed Abdulrahman Alomar[4], Saud Ahmed Mohammed Alzahrani[5], Hassah Fahad Buayshah[6], Abdulhakim Mohammed Badawi[7]

[1] College of Medicine, Taif University, Taif, Saudi Arabia
[2] College of Medicine, King Khalid University, Abha, Saudi Arabia
[3] Aseer Hospital, Abha, Saudi Arabia
[4] College of Medicine and Surgery, King Faisal University, Dhahran, Saudi Arabia
[5] Eastern Health Cluster, Dhahran, Saudi Arabia
[6] College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia
[7] College of Medicine, Shaqra University, Riyadh, Saudi Arabia
*Corresponding Author: Mashael Saad Alotaibi, Email: mashael88000@gmail.com

ABSTRACT

Background: Osteoporosis is a multifactorial skeletal disease, which is marked by decreased bone mineral density (BMD) and increased susceptibility to fractures, and genetic factors contribute to a significant share of inter individual variation in bone mass. Despite the fact that many molecular variants have been associated with the susceptibility of osteoporosis, the uniformity and clinical implication of these associations are yet to be fully established. The purpose of this systematic review was to review the available evidence on genetic polymorphisms and BMD outcomes and osteoporosis risk.

Methodology: A systematic literature review was performed in PubMed, Scopus, Embase, Web of Science, and Cochrane Library to find original genetic association studies comparing molecular variants to BMD or osteoporosis. Studies that used human population as the subject of observation and reported genotypic data that used quantitative BMD or fracture outcomes were included. Conference abstracts, reviews, meta-analyses and animal studies were excluded. Information was obtained on the characteristics of the study, genes of interest, skeletal locations that were evaluated, and reported associations. The quality of methodology was assessed with the help of standardized criteria, and the results were synthesized on a qualitative level.

Results: Nine of the eligible studies with over 11,000 participants who were of Asian and European origin were included. Regular correlations were found between the polymorphisms in the important bone regulatory genes and lower BMD. TNFRSF11B (osteoprotegerin) variants were repeatedly associated with reduced lumbar spine BMD and high fracture risk, whereas LRP5 variants were strongly associated with decreased spine and femoral neck BMD. Other VDR, FGFR1, FABP3, and TIMP2 variants were linked to site-specific loss of BMD and risk of a fracture. The majority of genetic influences were small but directional in populations.

Conclusion: Genetic polymorphisms in a variety of bone remodeling pathways play an important role in the variation of BMD and osteoporosis susceptibility. These results endorse a polygenic theory of skeletal fragility and emphasize the possibility of the use of genetic profiling in individual risk assessment and prevention measures.

INTRODUCTION

Osteoporosis is a significant health issue of the population that is marked by a decrease in bone mass, microarchitectural loss, and the risk of fragility fractures [1,2]. It impacts hundreds of millions of people across the globe and is a major cause of morbidity, disability and spending on healthcare, especially the postmenopausal women and the aging population [3]. The bone mineral density (BMD) is the most common quantitative measure of skeletal strength and the most commonly used predictor of fracture risk [4,5]. Though environmental factors like nutrition, physical activity and hormonal status play a significant role in bone health, the estimates of heritability indicate that 60-80 percent of the variance in BMD is genetically controlled [6,7].

In the last twenty years, molecular genetics have made significant contributions to the knowledge of the genetic makeup of osteoporosis [8]. Many candidate gene studies and genome-wide association studies (GWAS) have found polymorphisms in genes in bone remodeling pathways, such as those controlling osteoblast differentiation, osteoclastic activity, calcium homeostasis and hormonal signaling [9,10]. Gene variants of LRP5, VDR, ESR1, COL1A1, RANKL, OPG, and WNT signaling factors have been recurrently found to have a role in modulating bone mass density, bone turnover, and bone fragility [11,12]. Nevertheless, the reported associations in the studies are heterogeneous in nature, which includes the differences in the study design, ethnicity, skeletal sites, genotyping technique, and confounding variables [13].

The clinical translation of these findings has not been realized despite the increasing amount of genetic association research. The discrepancies in the magnitude of the effect, the inability to replicate the effects across populations, and the small role that individual polymorphisms play in the total fracture risk remain as obstacles in the creation of effective genetic risk models. In addition, the relative role played by individual molecular variants in site-specific BMD results and in their interplay with environmental exposures are not fully determined.

In this regard, an overall review of the existing evidence is justified to explain the quality and reliability of the relationships between genetic polymorphisms and predisposition to osteoporosis. This review aims to present a unified model of understanding the genetic determinants of osteoporosis by combining molecular genetics and clinical bone phenotypes and guide future research on the subject to focus on individualized risk prediction and prevention plans.

METHODOLOGY

This systematic review was done in line with the best methodological practices of evidence synthesis and adherence to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The extensive literature search was conducted to find the appropriate studies that assessed the relationship between genetic polymorphisms and susceptibility to osteoporosis, especially the results of bone mineral density. PubMed, Scopus, Web of Science, Embase, and Cochrane Library electronic databases were searched systematically since the beginning of their existence to the latest date possible. The search strategy was based on the use of controlled vocabulary and free-text words associated with osteoporosis, bone mineral density, genetic polymorphisms, single nucleotide polymorphisms, molecular variants as well as fracture risk. Manual screening of reference lists of eligible articles and relevant reviews was done to guarantee completeness of the retrieval.

The selection of eligible studies was based on pre-established inclusion and exclusion criteria. Case-control, cohort, and cross-sectional observational studies that assessed the relationship between genetic polymorphisms and the BMD measurements or diagnosis of osteoporosis in human populations were included. The studies had to report genotypic or allelic distributions and give the quantitative BMD data or standardized diagnostic criteria of osteoporosis. The exclusion criteria were reviews, editorials, abstracts of conferences without complete data, animal research, and studies that did not provide enough information about the methods. Titles and abstracts were independently screened by two reviewers after which full-text evaluation of potentially relevant articles was conducted, and any discrepancy was resolved by discussion or involving a third reviewer.

The extraction of data was done through a standardized form so as to maintain consistency and accuracy. The variables that were extracted were first author, year of publication, country, study design, sample size, characteristics of the participants, skeletal sites measured, genotyping method, investigated polymorphisms, BMD measurement methods and reported effect estimates. Adjusted measures of association and confounding variables information were also noted when possible. The association between particular genetic variants and BMD values or the risk of osteoporosis was the primary outcome of interest, and fracture incidence and bone turnover indicators were the secondary outcomes.

The quality of methodology of included studies was evaluated with the help of the proper appraisal instrument on the basis of the study design. The Newcastle-Ottawa Scale was used to assess case-control and cohort studies on the basis of selection, comparability, and outcome or exposure assessment. A quality score was given to each study and the study was classified into low, moderate and high quality methodology. A sensitivity analysis was to be conducted to investigate the impact of quality of the studies on the general interpretation of the findings.

The synthesis of data was largely qualitative since genetic variants, outcome measures and population characteristics were expected to be heterogeneous. Polymorphism-bone outcome associations were described descriptively, considering consistency of direction and magnitude of effects across studies and ethnic groups.

RESULTS

In the final synthesis, a total of nine studies (Figure 1), that are eligible genetic association studies were included and they include a combined sample of over 11,000 individuals in various populations (Table 1). Most of the studies were carried out on postmenopausal females of East Asian and European cohort with the population of China, Japan, Spain, Slovakia, Hungary and UK being represented [14-22]. The sizes of the samples were quite different as well, with small candidate gene studies consisting of less than 200 participants, and large-scale genome-wide association studies consisting of more than 8,000 participants [20]. The majority of the studies were based on cross-sectional or case-control genetic association designs, and one large study used a genome-wide method to determine susceptibility loci [20].

In the literature, the predominant studies that were conducted were on candidate genes related to bone remodeling and signaling pathways. Variations in the TNFRSF11B (osteoprotegerin) and LRP5 genes, which are the key players in osteoclast regulation and Wnt signaling, respectively, were most commonly studied as loci [14-18, 20]. Other polymorphisms were also evaluated in hormonal signaling and extracellular matrix regulating genes, such as VDR, CTR, FGFR1, FABP3, TIMP2, and WDSOF1 [1922]. BMD was regularly assessed by dual-energy X-ray absorptiometry of skeletal areas of clinical interest, the lumbar spine and the femoral neck, which offers a standardized phenotypic framework in genetic association studies.

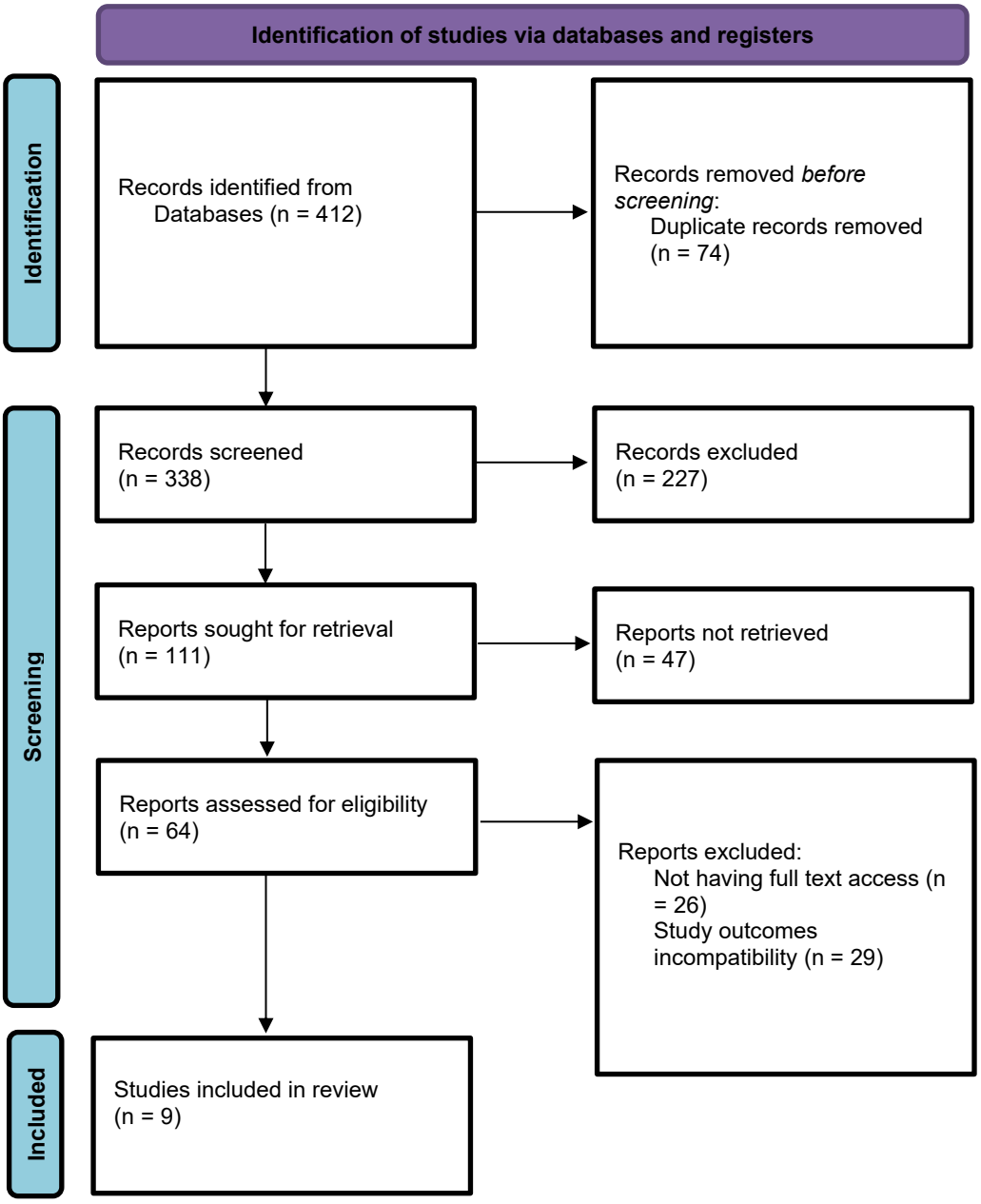

Figure 1: PRISMA flow for including studies

Table 1. General Characteristics of Included Genetic Association Studies (N = 9)

Author, Year)	Population (Ethnicity / Sex)	Sample Size	Study Design	Genes / Polymorphisms Studied
Feng G et al., 2012 [14]	Chinese postmenopausal women	352	Cross-sectional genetic association	TNFRSF11B (OPG) g.23276G>A
Song J et al., 2013 [15]	Chinese postmenopausal women	399	Cross-sectional genetic association	TNFRSF11B (OPG) g.2264T>C, g.27676A>C
Boroňová I et al., 2015 [16]	Slovak postmenopausal women	327	Case–control gen assoc. + fracture outcomes	TNFRSF11B rs3134069, A163G, G1181C
Urano-Shiraki et al., 2004 [17]	Japanese postmenopausal women	308	Cross-sectional association	LRP5 IVS17-1677C>A

Al-Amoodi M et al., 2018 [18]	Spanish Caucasian adults	168	Genetic association	LRP5 rs3736228
Bandrés et al., 2005 [19]	Spanish postmenopausal women	177	Cohort gen assoc.	VDR polymorphisms (Ff/ff genotypes), CTR polymorphisms
Richards J et al, 2008 [20]	UK/European adults	8557	Genome-wide association study	LRP5 rs3736228, TNFRSF11B rs4355801
Urano T et al., 2010 [21]	Japanese postmenopausal women	750	Association study	WDSOF1 rs1370005
Lazary A et al. 2008 [22]	Hungarian postmenopausal women	360	Candidate gene	FGFR1, FABP3, TIMP2 SNPs

Taken together, the studies included showed uniform links among numerous genetic polymorphisms and variation in bone mineral density, and various variants increased the vulnerability to low BMD and osteoporosis (Table 2). The TNFRSF11B gene variants were repeatedly reported to be correlated with lower lumbar spine BMD and higher risk of osteoporosis or fracture, with minor alleles being consistently correlated with poor skeletal phenotype in various populations [14-16]. These results confirm the regulatory importance of osteoprotegerin in the bone resorption process by osteoclasts.

In the same way, the LRP5 gene polymorphisms were strongly and consistently linked to both lumbar spine and femoral neck BMD, and the risk alleles were linked to much lower BMD levels in several cohorts [17-19]. Genome-wide evidence also supported the role of LRP5 and TNFRSF11B loci in population skeletal variation [20]. Genetic differences in hormonal and growth factor-related genes, such as VDR and FGFR1 were also related to site-specific decreases in spinal and hip BMD, reflecting the effect of endocrine and signalling pathways on bone metabolism [19,21]. Moreover, FABP3 and TIMP2 polymorphisms were associated with both decreasing bone mineral density and augmenting the fracture vulnerability, which suggested that these proteins might have more functions in bone quality and structure than merely mineral density [22]. All in all, the cumulative evidence suggests that the genetic differences between individuals in terms of BMD and osteoporosis risk are based on the genetic variation that occurs in several regulatory pathways.

Table 2. Molecular Variants and Bone Mineral Density (BMD) Outcomes

Study (First Author, Year)	Gene / Variant	Outcome (BMD Measure, Site)	Association with BMD / Osteoporosis	Effect (Direction / P-value)
Feng G et al., 2012 [14]	**TNFRSF11B (OPG) g.23276G>A**	Lumbar spine BMD	A-allele associated with lower BMD	GG > GA/AA BMD; A-allele ↑ osteoporosis risk
Song J et al., 2013 [15]	**TNFRSF11B g.2264T>C**	Lumbar spine BMD	C-allele associated with lower BMD	TT > TC/CC BMD at spine (P significant)
Song J et al., 2013 [15]	**TNFRSF11B g.27676A>C**	Spine BMD	C-allele associated with lower BMD	AA > AC/CC at spine (P significant)
Boroňová I et al., 2015 [16]	**TNFRSF11B rs3134069 (T245G)**	Spine L1–L4 BMD & fractures	T245G associated with lower BMD and increased fractures	Lower BMD and fracture associations
Urano-Shiraki et al., 2004 [17]	**LRP5 IVS17-1677C>A**	Lumbar & total body BMD	A-allele carriers had lower BMD	CA/AA lower vs CC ($P<0.05$)
Al-Amoodi M et al., 2018 [18]	**LRP5 rs3736228 (Ala1330Val)**	Lumbar spine & femoral neck BMD	Risk T allele associated with lower BMD	BMD decrease at lumbar & FN ($p<10^{-4}$)
Bandrés et al., 2005 [19]	**LRP5 rs3736228**	BMD by DXA/QUS	Risk allele associated with lower BMD	Lower BMD in variant carriers
Richards J et al, 2008 [20]	**VDR (FF/Ff/ff)**	Spine, hip BMD	FF genotype highest BMD; ff lowest	Significant genotype-BMD differences

Urano T et al., 2010 [21]	**FGFR1 rs6996321**	Spine BMD	A allele linked with lower spine BMD	Significant association
Lazary A et al. 2008 [22]	**FABP3 rs10914367**	Hip BMD	'A' allele linked with lower hip BMD	P=0.028
Lazary A et al. 2008 [22]	**TIMP2 rs9900972**	Fracture risk (proxy phenotype)	'A' allele increased non-vertebral fracture risk	OR≈2.06

In general, the quality of the methodology of the utilized studies was moderate to high. The majority of the studies showed that the risk of bias in the selection of participants and the assessment of the outcome was low as the studies used clearly defined populations, a standardized dual-energy X-ray absorptiometry measure, and validated genotyping methods [14-22]. The comparability between the study groups was generally sufficient, and some of the studies have adjusted major confounders, including age, body mass index, and menopausal status [16,20]. The overall risk of bias was the least in the large genome-wide association study because of its large sample size and an elaborate adjustment plan [20]. Small candidate gene studies were the most common studies that had moderate risk of bias which could be largely explained by small sample sizes and inability to control possible confounding factors [18,22]. None of the studies showed high risk of bias in various areas, which implied that the entire body of evidence was methodologically sound and could be used to conduct qualitative synthesis (Table 3).

Table 3: Risk of Bias Assessment of Included Genetic Association Studies Using the Newcastle–Ottawa Scale

Study	Selection	Comparability	Exposure / Outcome Assessment	Overall Risk of Bias
Feng G et al., 2012 [14]	Low	Moderate	Low	Low–Moderate
Song J et al., 2013 [15]	Low	Moderate	Low	Low–Moderate
Boroňová I et al., 2015 [16]	Low	High	Low	Low
Urano-Shiraki et al., 2004 [17]	Low	Moderate	Low	Low–Moderate
Al-Amoodi M et al., 2018 [18]	Moderate	Moderate	Low	Moderate
Bandrés et al., 2005 [19]	Low	Moderate	Low	Low–Moderate
Richards J et al., 2008 [20]	Low	High	Low	Low
Urano T et al., 2010 [21]	Low	Moderate	Low	Low–Moderate
Lazary A et al., 2008 [22]	Low	Moderate	Moderate	Moderate

DISCUSSION

The current systematic review shows that genetic polymorphisms in major bone remodeling regulatory pathways are always correlated with the difference in bone mineral density and osteoporosis vulnerability. Genetic variants in genes that regulate osteoclasts, Wnt signaling, hormonal signaling and extracellular matrix remodeling had reproducible relations with site-specific BMD results in ethnically diverse groups. These results support the notion that osteoporosis is a very polygenic disease where a combination of several low-penetrance variants can determine bone strength and the risk of fracture [2,23].

Polymorphisms in the TNFRSF11B gene that encode osteoprotegerin were among the most repeatedly associated with lower lumbar spine BMD and higher risk of fracture. Osteoprotegerin is a decoy receptor of receptor activator of nuclear factor- 0 ligand (RANKL), which suppresses the differentiation of osteoclasts and bone resorption [24,25]. It has been demonstrated by both functional and experimental studies that changes in the RANK-RANKL-OPG axis destabilize the bone formation and resorption balance, resulting in increased bone loss and structural fragility [26,27]. These findings of minor TNFRSF11B alleles with reduced BMD are thus biologically feasible and consistent with previous data on impaired OPG signaling and postmenopausal bone loss and fracture risk [28,29].

Alternations in the LRP5 gene became another significant predictor of skeletal phenotypes in the involved studies. LRP5 is a co-receptor of the canonical Wnt/ -catenin pathway which is a key in osteoblast differentiation and bone

formation. Loss-of-function mutations that cause osteoporosis-pseudoglioma syndrome have been reported to have rare loss-of-function mutations in LRP5, whereas gain-of-function mutations cause high bone mass phenotypes [30,31]. Population-based cohorts have repeatedly reported common polymorphisms, including the rs3736228, to be associated with less BMD and higher risk of fracture [32,33]. The overall direction of effect in the various populations in the current synthesis justifies the idea that minor adjustment of Wnt signaling plays a significant role in the interindividual difference in peak bone mass and age-related bone loss.

Among the major associations was the hormonal signaling pathways, especially via polymorphic genes in vitamin D receptor (VDR). The VDR variants and their effects on BMD have been widely studied and various studies have found to have genotype-specific differences in calcium absorption, bone turnover, and skeletal mass [34]. The current results, which show greater BMD in carriers with positive VDR genotypes are in line with the known functions of vitamin D signaling in calcium homeostasis and skeletal mineralization. These findings also indicate that the genetic background interacts with endocrine regulation to establish the risk of osteoporosis.

In addition to classical pathways, it was found that polymorphisms in growth factor related and matrix regulation genes such as FGFR1, FABP3, and TIMP2 were related to decreased BMD and increased fracture risk. Signaling of fibroblast growth factor has been implicated in the proliferation and skeletal development of the osteoblasts, and tissue inhibitors of metalloproteinases mediate the remodeling and microarchitecture of the bone [35]. The associations observed indicate that genetic variation in bone quality and matrix integrity can have an independent effect on the risk of fracture, even in the absence of areal BMD, something that is beginning to be accepted in the pathophysiology of osteoporotic fractures [36].

Although the relationships were generally consistent, the heterogeneity between studies was observed in the forms of population ancestry, sites of skeletal analysis, and the extent of genetic effects. The difference in reported associations could be partly due to ethnic differences in allele frequencies and patterns of linkage disequilibrium and this has been well-documented in the genetics of osteoporosis [37]. Moreover, the majority of the polymorphisms had moderate effects on BMD, which highlights the point that no single polymorphism can be used to predict the risk of osteoporosis on its own. This finding is consistent with the existing models that suggest that multifactoriality of skeletal fragility is better explained by cumulative genetic risk scores and by gene-environment interactions [38].

CONCLUSION

In conclusion, the current synthesis indicates the key role of genetic variation in a variety of biological pathways in predisposing to osteoporosis. The overlap of results on osteoclast control, Wnt signaling, hormonal pathways and matrix remodeling highlights the complexity of bone metabolism and the necessity of integrative genetic models. The translation of genetic findings into individual fracture risk prediction and preventive measures can be achieved in future studies that are based on large multi-ethnic cohorts, functional validation, and polygenic risk profiling.

REFERENCES

1. Castellani C, De Martino E, Scapato P. Osteoporosis: Focus on bone remodeling and disease types. *BioChem*. 2025;5(3):31. doi:10.3390/biochem5030031
2. Pouresmaeili F, Dehghan BK, Kamarehei M, Meng GY. A comprehensive overview on osteoporosis and its risk factors. *Therapeutics and Clinical Risk Management*. 2018;Volume 14:2029-2049. doi:10.2147/tcrm.s138000
3. Kenzhegazova GK, Baspakova A, Umbetova AA. Osteoporosis: A comprehensive review of epidemiology, impact on quality of life, and treatment strategies. *West Kazakhstan Medical Journal*. 2025;67(2):177-187. doi:10.18502/wkmj.v67i2.16570
4. Haseltine KN, Chukir T, Smith PJ, Jacob JT, Bilezikian JP, Farooki A. Bone mineral density: Clinical relevance and quantitative assessment. *Journal of Nuclear Medicine*. 2020;62(4):446-454. doi:10.2967/jnumed.120.256180
5. Kranioti EF, Bonicelli A, García-Donas JG. Bone-mineral density: clinical significance, methods of quantification and forensic applications *Research and Reports in Forensic Medical Science*. 2019;Volume 9:9-21. doi:10.2147/rrfms.s164933
6. Mikkola TM, Sipilä S, Rantanen T, et al. Genetic and Environmental influence on structural strength of Weight-Bearing and Non–Weight-Bearing Bone: a twin study. *Journal of Bone and Mineral Research*. 2007;23(4):492-498. doi:10.1359/jbmr.071205
7. Abdollahi S, Taheri F, Lahijan ASN, Shoga SH, Didehban A, Doaei S. Genetics and Vitamin D Interactions in Osteoporosis: A Path to Precision Medicine. *Journal of Cellular and Molecular Medicine*. 2025;29(16):e70780. doi:10.1111/jcmm.70780
8. Amroodi MN, Maghsoudloo M, Amiri S, et al. Unraveling the molecular and immunological landscape: Exploring signaling pathways in osteoporosis. *Biomedicine & Pharmacotherapy*. 2024;177:116954. doi:10.1016/j.biopha.2024.116954

9. Kim J, Kim BY, Lee JS, et al. UBAP2 plays a role in bone homeostasis through the regulation of osteoblastogenesis and osteoclastogenesis. *Nature Communications*. 2023;14(1):3668. doi:10.1038/s41467-023-39448-8
10. Anouti FA, Taha Z, Shamim S, Khalaf K, Kaabi LA, Alsafar H. An insight into the paradigms of osteoporosis: From genetics to biomechanics. *Bone Reports*. 2019;11:100216. doi:10.1016/j.bonr.2019.100216
11. Zurel F, Bux H, Diveli A, Rashid Z. Genetic Influences and Targeted Treatments in Osteoporosis: A Systematic review. *Cureus*. 2025;17(7):e87436. doi:10.7759/cureus.87436
12. Oton-Gonzalez L, Mazziotta C, Iaquinta MR, et al. Genetics and epigenetics of bone remodeling and metabolic bone diseases. *International Journal of Molecular Sciences*. 2022;23(3):1500. doi:10.3390/ijms23031500
13. Liu J, Lewinger JP, Gilliland FD, Gauderman WJ, Conti DV. Confounding and Heterogeneity in Genetic Association Studies with Admixed Populations. *American Journal of Epidemiology*. 2013;177(4):351-360. doi:10.1093/aje/kws234
14. Feng G, Meng L, Wang H, et al. Single-nucleotide polymorphism of the osteoprotegerin gene and its association with bone mineral density in Chinese postmenopausal women. *Journal of Pediatric Endocrinology and Metabolism*. 2012;25(11-12):1141-1144. doi:10.1515/jpem-2012-0274
15. Song JF, Jing ZZ, Hu W, Su YX. Association between single nucleotide polymorphisms of the osteoprotegerin gene and postmenopausal osteoporosis in Chinese women. *Genetics and Molecular Research*. 2013;12(3):3279-3285. doi:10.4238/2013.september.3.4
16. Boroňová I, Bernasovská J, Mačeková S, et al. TNFRSF11B gene polymorphisms, bone mineral density, and fractures in Slovak postmenopausal women. *Journal of Applied Genetics*. 2014;56(1):57-63. doi:10.1007/s13353-014-0247-4
17. Urano T, Shiraki M, Ezura Y, et al. Association of a single-nucleotide polymorphism in low-density lipoprotein receptor-related protein 5 gene with bone mineral density. *Journal of Bone and Mineral Metabolism*. 2004;22(4):341-345. doi:10.1007/s00774-003-0492-9
18. H. Al-Amoodi, J, Jones, Lee, McKenzie, Miller C, Zeller. The association of polymorphism RS3736228 within the LRP5 gene with bone mineral density in a cohort of Caucasian young adults. *Health Sciences Research Commons*. 2019;149.
19. Bandrés E, Pombo I, González-Huarriz M, Rebollo A, López G, García-Foncillas J. Association between bone mineral density and polymorphisms of the VDR, ERα, COL1A1 and CTR genes in Spanish postmenopausal women. *Journal of Endocrinological Investigation*. 2005;28(6):312-321. doi:10.1007/bf03347196
20. Richards J, Rivadeneira F, Inouye M, et al. Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. *The Lancet*. 2008;371(9623):1505-1512. doi:10.1016/s0140-6736(08)60599-1
21. Urano T, Shiraki M, Usui T, Sasaki N, Ouchi Y, Inoue S. Identification of non-synonymous polymorphisms in the WDSOF1 gene as novel susceptibility markers for low bone mineral density in Japanese postmenopausal women. *Bone*. 2010;47(3):636-642. doi:10.1016/j.bone.2010.06.017
22. Lazáry Á, Kósa JP, Tóbiás B, et al. Single nucleotide polymorphisms in new candidate genes are associated with bone mineral density and fracture risk. *European Journal of Endocrinology*. 2008;159(2):187-196. doi:10.1530/eje-08-0021
23. Del Real Á, Cruz R, Martínez JMO, Hernández JL, De La Madrid CVD, Moral JAR. Polygenic risk of bone fractures in Spanish women with osteoporosis. *Revista De Osteoporosis Y Metabolismo Mineral*. Published online January 1, 2023. doi:10.20960/revosteoporosmetabminer.00014
24. Grimaud E, Soubigou L, Couillaud S, et al. Receptor activator of nuclear factor KB ligand (RANKL)/Osteoprotegerin (OPG) ratio is increased in severe osteolysis. *American Journal of Pathology*. 2003;163(5):2021-2031. doi:10.1016/s0002-9440(10)63560-2
25. Kostenuik P. Osteoprotegerin and RANKL regulate bone resorption, density, geometry and strength. *Current Opinion in Pharmacology*. 2005;5(6):618-625. doi:10.1016/j.coph.2005.06.005
26. Kohli S, Kohli V. Role of RANKL-RANK/osteoprotegerin molecular complex in bone remodeling and its immunopathologic implications. *Indian Journal of Endocrinology and Metabolism*. 2011;15(3):175. doi:10.4103/2230-8210.83401
27. Zhang Y, Liang J, Liu P, Wang Q, Liu L, Zhao H. The RANK/RANKL/OPG system and tumor bone metastasis: Potential mechanisms and therapeutic strategies. *Frontiers in Endocrinology*. 2022;13:1063815. doi:10.3389/fendo.2022.1063815
28. Kotrych K, Wojtuń M, Górska A, et al. The influence of clinical factors and genetic variants of COL1A1 and TNFRSF11B on bone mineral density in postmenopausal women. *International Journal of Molecular Sciences*. 2025;26(18):8894. doi:10.3390/ijms26188894
29. González-Mercado A, Sánchez-López J, Perea-Díaz F, et al. Association of polymorphisms of the TNFRSF11B and TNFSF11 genes with bone mineral density in postmenopausal women from western Mexico. *Archives of Medical Science*. 2019;15(5):1352-1356. doi:10.5114/aoms.2019.87410
30. Levasseur R, Lacombe D, De Vernejoul MC. LRP5 mutations in osteoporosis-pseudoglioma syndrome and high-bone-mass disorders. *Joint Bone Spine*. 2004;72(3):207-214. doi:10.1016/j.jbspin.2004.10.008

31. Laine CM, Chung BD, Susic M, et al. Novel mutations affecting LRP5 splicing in patients with osteoporosis-pseudoglioma syndrome (OPPG). *European Journal of Human Genetics*. 2011;19(8):875-881. doi:10.1038/ejhg.2011.42
32. Xu GY, Qiu Y, Mao HJ. Common polymorphism in theLRP5Gene may increase the risk of bone fracture and osteoporosis. *BioMed Research International*. 2014;2014:1-13. doi:10.1155/2014/290531
33. Ciubean AD, Ungur RA, Irsay L, et al. Polymorphisms of FDPS, LRP5, SOST and VKORC1 genes and their relation with osteoporosis in postmenopausal Romanian women. *PLoS ONE*. 2019;14(11):e0225776. doi:10.1371/journal.pone.0225776
34. Zhang L, Yin X, Wang J, et al. RETRACTED ARTICLE: Associations between VDR Gene Polymorphisms and Osteoporosis Risk and Bone Mineral Density in Postmenopausal Women: A systematic review and Meta-Analysis. *Scientific Reports*. 2018;8(1):981. doi:10.1038/s41598-017-18670-7
35. Guasto A, Cormier-Daire V. Signaling pathways in bone development and their related skeletal dysplasia. *International Journal of Molecular Sciences*. 2021;22(9):4321. doi:10.3390/ijms22094321
36. Adams DJ, Ackert-Bicknell CL. Genetic regulation of bone strength: a review of animal model studies. *BoneKEy Reports*. 2015;4:714. doi:10.1038/bonekey.2015.83
37. Marozik PM, Tamulaitiene M, Rudenka E, et al. Association of vitamin D receptor gene variation with osteoporosis risk in Belarusian and Lithuanian postmenopausal women. *Frontiers in Endocrinology*. 2018;9:305. doi:10.3389/fendo.2018.00305
38. Busse E, Lee B, Nagamani SCS. Genetic evaluation for monogenic disorders of low bone mass and increased bone fragility: What clinicians need to know. *Current Osteoporosis Reports*. 2024;22(3):308-317. doi:10.1007/s11914-024-00870-6