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Systematic Review

Genetic influence on osteoporosis and fracture risk: Outcome of genome-wide association studies – A systematic review

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ABSTRACT

This systematic review aimed to identify genome-wide association studies (GWASs) highlighting the genes and single-nucleotide polymorphisms linked to osteoporosis and fragility fracture risk. We searched the search engines EMBASE, MEDLINE, Scopus, Web of Science, Science Citation Index, and Cochrane database of systematic reviews between 2005 and May 2022. The articles were reviewed individually for risk of bias and found no variances in the papers designated for analysis. We analyzed 63 studies with 1,326,798 patients, which included postmenopausal and premenopausal women. Thirty-one studies used dual-energy x-ray absorptiometry (DXA) for the diagnosis. Three studies used ultrasonography, and one used peripheral quantitative computed tomography (pQCT) to diagnose osteoporosis. For the risk of fragility fractures, 15 studies with 744,123 were analyzed, which used DXA in 12, two studies of ultrasonography, and one of radiography. Three studies were reported in premenopausal women and three in children with 18,203 subjects. Our analysis showed that 150 genes, 515 loci that target bone mineral density and 15 loci that increase fracture risk in osteoporosis have been identified. Osteoporosis and fragility fractures are common in the Saudi Arabian population. The GWAS gives an understanding of the genetic basis of low bone density, osteoporosis, and fragility fractures. The GWAS data can provide new pathways to understanding the etiology of osteoporosis and a route to prevention and optimum treatment. Hence, we believe that we should conduct GWASs on osteoporosis sooner rather than later so that we can advise at-risk individuals to change their lifestyle so that they can limit complications of osteoporosis and related complications.

Keywords: Bone mineral density, Fragility fractures, Genome-wide association study, Human genome project, Osteoporosis

INTRODUCTION

Osteoporosis is a silent and far-reaching skeletal disease that affects over ~200 million people in the World. The condition is characterized by deterioration of the microarchitecture of bone, which leads to fragility fractures.[1,2] By 2050, over 212 million people will suffer from low bone mass.[3] The economic burden has increased in billions with the aging population, and the annual cost of treating fragility fractures in the United States has risen to $17 billion.[4,5] In contrast, by

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2035, such treatment will cost nearly $19 billion in China.[6] Apart from a lack of estrogen in women and testosterone in men and environmental factors, 80% of osteoporosis is due to genetic influence.[2,7]

The human genome project (HGP) was undertaken to identify, map, and sequence all of the human body's genes, but genome-wide association studies (GWASs) discovered many genes and thousands of single nucleotide polymorphisms (SNPs), which influence many diseases including osteoporosis and fragility fractures.[8-13] If GWAS is not performed properly and cannot identify the genes and SNPs that influence the diseases, this may result in statistically significant analysis with low odds ratios that may not give a convincing contribution. The inspiration to perform this analysis came from the GWAS in other parts of the world giving a strong indication of the genetic influence on bone mineral density (BMD) and fragility fractures. In this context, if people know that they carry genes and SNPs that will cause osteoporosis and fragility fractures, they could change their lifestyle, gain more BMD, and reduce the risk of osteoporosis and fragility fractures.

This review aimed to identify GWASs in the Middle East and the rest of the World highlighting the genes and SNPs that decrease the achievement of BMD and increase the risk of osteoporosis and fragility fractures.

MATERIALS AND METHODS

This is a systematic review in which we searched between 2005 and May 2022 all relevant databases such as EMBASE, Cochrane database of Systematic Reviews, MEDLINE, Science Citation Index, Scopus, and Web of Science with keywords of osteoporosis, BMD, and fragility fractures. In the context of GWASs, investigators will first identify locations of the genome that highlight a strong striking link to the traits in question, i.e., in the discovery cohort, areas or specific markers in which variation is more common than in the controls. The standard steps of conducting GWAS for any disease are to collect samples and traits, gather genotype samples, test statistically each SNP for association of the disease, tabulate the results, and simulate the data.

The criteria for inclusion of studies for analysis were articles involving patients with the presence or absence of the gene and SNPs related to osteoporosis, BMD and fragility fractures, case–control or family-based genetic association studies, diagnosis of osteoporosis, and fragility fractures using a standard classification system that was published in the English language in HGP, GWAS, target genes, and clinical translation. The criteria for exclusion were review articles and correspondence.

The authors reviewed all the articles independently and then together, and there was no discrepancy in the papers selected for the review. This analysis was done as per PRISMA guidelines.[14]

RESULTS

We analyzed 63 studies and 1,326,798 patients, which included those on postmenopausal and premenopausal patients [Figure 1]. The data analyzed of postmenopausal patients, which numbered 35 studies with 564,472 patients [Table 1]. Thirty-one studies used DXA for the diagnosis, three used ultrasonography, and one study used peripheral quantitative computed tomography (pQCT) to diagnose osteoporosis. Table 2 gives the data of analysis of fragility fractures and osteoporosis. Fifteen studies with 744,123 used DXA in 12, two studied ultrasonography, and one used radiography. Table 3 shows three studies in premenopausal women and three in children with 18,203 subjects. Most of the studies were conducted among Europeans, North Americans, Japanese, Chinese, Africans, Koreans, and East Asian ancestry.

The studies have identified 150 genes and 515 SNPs, which are directly linked to BMD and Osteoporosis. Fifteen loci have been identified, which indicate the risk of fragility fractures.

DISCUSSION

Our review shows that GWAS has produced clear and reproducible findings in which more than 150 genes are implicated in the risk of individuals developing osteoporosis and its complications. The diagnosis of osteoporosis centers around the reading of BMD of reduction of more than 2.5 standard deviations from the normal mean of 35 years adult (T-Score), which is diagnosed as osteoporosis. Most

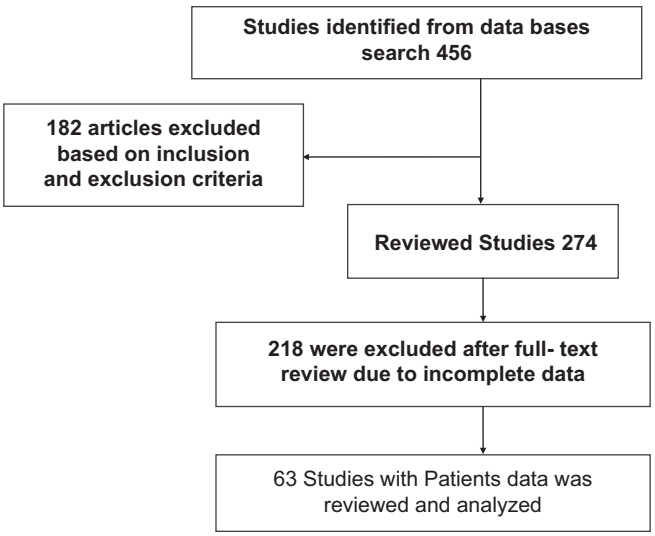

Figure 1: PRISMA flow chart of the review.

Table 1: List of published GWAS in adults on BMD, osteoporosis analyzed.

S. No.	Authors	Number of patients	Method used for assessment
1.	Kiel *et al*. (2007)[15]	1117	DXA
2.	Xiong *et al*. (2009)[16]	9858	DXA
3.	Liu *et al*. (2009)[17]	4355	DXA
4.	Rivadeneira *et al*. (2009)[18]	19,195	DXA
5.	Guo *et al*. (2010)[19]	10,352	DXA
6.	Guo *et al*. (2010)[20]	2557	DXA
7.	Hsu *et al*. (2010)[21]	7633	DXA
8.	Tan *et al*. (2010)[22]	1628	DXA
9.	Paternoster *et al*. (2010)[23]	3835	DXA
10	Kou *et al*. (2011)[24]	2279	DXA
11.	Duncan *et al*. (2011)[25]	20,898	DXA
12.	Lei *et al*. (2012)[26]	3355	DXA
13.	Liu *et al*. (2012)[27]	24,763	PQCT
14.	Guo *et al*. (2013)[28]	3913	DXA
15.	Deng *et al*. (2013)[29]	5130	DXA
16.	Zhang *et al*. (2014)[30]	15,871	DXA
17.	Tan *et al*. (2015)[31]	2845	DXA
18.	Mullin *et al*. (2016)[32]	5654	ULTRA
19.	Hwang *et al*. (2016)[33]	7263	DXA
20.	Choi *et al*. (2016)[34]	2286	DXA
21.	Pei *et al*. (2016)[35]	7513	DXA
22.	Pei *et al*. (2016)[36]	2874	DXA
23.	Mullin *et al*. (2017)[37]	13,749	ULTRA
24.	Villalobos-Comparán *et al*. (2017)[38]	420	DXA
25.	Kemp *et al*. (2017)[39]	142,487	ULTRA
26.	Peng *et al*. (2017)[40]	53,236	DXA
27.	Lu *et al*.(2017)[41]	2069	DXA
28.	Pei *et al*. (2018)[42]	40,491	DXA
29.	Lin *et al*. (2018)[43]	49,988	DXA
30.	Qiu *et al*. (2018)[44]	5905	DXA
31.	Gregson *et al*. (2018)[45]	30,970	DXA
32.	Naito *et al*. (2018)[46]	173	DXA
33.	Liang *et al*. (2018)[47]	3404	DXA
34.	Styrkarsdottir *et al* (2019)[48]	50,231	DXA
35.	Zhang *et al*. (2020)[49]	6175	DXA

DXA: Dual-energy X-ray absorptiometry, PQCT: Peripheral quantitative computed tomography, GWAS: Genome-wide association studies, BMD: Bone mineral density

Table 2: List of published GWAS in adults on fragility fractures analyzed.

S. No.	Authors	Number of patients	Method used for assessment
1.	Richards *et al*. (2008)[50]	6463	DXA
2.	Styrkarsdottir *et al*. (2008)[51]	7925	DXA
3.	Guo *et al*. (2010)[19]	10,352	DXA
4.	Kung *et al*. (2010)[52]	18,098	DXA
5.	Estrada *et al*. (2012)[53]	31,016	DXA
6.	Zheng *et al*. (2012)[54]	2023	DXA
7.	Hwang *et al*. (2013)[55]	1119	DXA
8.	Zheng *et al*. (2013)[56]	8604	DXA
9.	Taylor *et al*. (2016)[57]	10,305	DXA
10.	Styrkarsdottir *et al*. (2016)[58]	10,389	DXA
11.	Styrkarsdottir *et al*. (2016)[59]	2636	DXA
12.	Kim (2018)[60]	59,378	ULTRA
13	Trajanoska *et al*. (2018)[61]	147,200	XRAY
14.	Alonso *et al*. (2018)[62]	2181	DXA
15.	Morris *et al*. (2019)[63]	426,824	ULTRA
		744,513	

DXA: Dual-energy X-ray absorptiometry, GWAS: Genome-wide association studies

Table 3: List of published GWAS in other groups analyzed.

S. No.	Authors	Number of patients	Method used for assessment
Premenopausal group			
1.	Tang *et al*. (2009)[64]	1089	DXA
2.	Koller *et al*. (2010)[65]	1524	DXA
3.	Koller *et al*. (2013)[66]	4061	DXA
Pediatric group			
4.	Timpson *et al*. (2009)[67]	7470	DXA
5.	Medina-Gomez *et al*. (2012)[68]	2660	DXA
6.	Chesi *et al*. (2015)[69]	1399	DXA

DXA: Dual-energy X-ray absorptiometry, GWAS: Genome-wide association studies

GWASs were carried out based on the BMD, a proven risk factor for osteoporosis and fragility fractures. Phenotype refers to an individual's visible traits and is fixed by both their genomic makeup and environmental factors. Both genetic and environmental factors influence the incidence of osteoporosis and fracture risk in a given population. The marvelous technique that GWAS performs is identifying genetic variants associated with a given phenotype, and the study estimates the risk of osteoporosis and fracture risk. At present, some gene-based tests have been developed to analyze multiple rare genetic variants associated with phenotypic traits.

For a long, it was known that genetics played a major role in the achievement of skeletal strength and the risk of osteoporosis.[70,71] This led to the study and identification of target genes, which increased the risk of osteoporosis. Before the era of GWAS, Stewart and Ralston,[72] in a review, reported at least 15 target genes that influence BMD and osteoporosis, but the studies reported by GWAS completely changed the concept of earlier detection of genetic predispositions to disease.

Guo *et al*.[19] reported the first osteoporosis-related GWAS in which a member of the aldehyde dehydrogenase gene

(*ALDH7A1*) was found to cause osteoporosis in the Chinese population, which was later replicated in Caucasian people. Initially, genetic influence on osteoporosis was studied in specific genes but GWAS was able to look for the whole genome in a large group of people and identified all the genes and even small variations of SNPs.

Many studies followed this concept, which confirmed beyond doubt the genetic influence on osteoporosis and fragility fractures. Initial GWASs prospectively looked at the variants of *LRP4*, *LRP5*, and *LRP6* genes in the Caucasian population and found that 2 SNPs (rs3736228, rs4988321) in the *LRP5* gene greatly influence the decrease in BMD and osteoporosis while no influence was observed by the SNP of *LRP4* and *LRP6* gene.[73-75]

Genes and SNPs affect BMD at the femoral neck or the lumbar spine, and some of them affect both sites. The GWAS found that polymorphisms of *CATSPERB* (rs1298989 and rs1285635), *PTH* gene (rs9630182, rs2036417, and rs7125774), and *IL21R* gene (rs7199138, rs8061992, and rs8057551) were strongly associated with BMD at femoral neck.[20,65] The influence of CATSPERB gene polymorphisms (rs1298989 and rs1285635) causing lower BMD had similar effects in multi-ethnic groups.[65] The GWASs in the premenopausal studies have also indicated various SNPs, which negatively impact the attainment of the BMD.[64-66] Tang *et al.*[64] reported that SNP (rs3747532) in the *CER1* gene not only decreases the BMD but also increases the risk of vertebral fractures. Furthermore, studies have shown that more candidate genes and SNPs affect BMD reaching genome-wide significance of a fixed P-value threshold of 5×10^{-8}. To date, 150 genes and 515 loci have been directly linked to BMD, osteoporosis, and fragility fractures.[21,30,52,53,76,77]

Most of the GWAS studies have been carried out in European, African, American, Asian, and Chinese populations where the reported incidence of osteoporosis is between 11% and 13%.[4,5] The reported incidence of osteoporosis among the Saudi Arabian population is more than twice that of the Caucasian population.[78] The Saudi Human Genome Program (SHGP) was established in 2014 and got the patronage of the Crown Prince for the 2030 vision, but unfortunately, not a single GWAS for osteoporosis was conducted in Saudi Arabia even though by 2050, osteoporosis-related femoral fractures alone will cost 35 billion Saudi Riyals.[78,79]

The only genetic study to date on osteoporosis revealed that the genetic makeup of the Saudi population related to osteoporosis and fragility fractures is different from that of the Western population.[80] Hence, it is appropriate to robustly recommend that it is time that SHGP undertake GWASs on osteoporosis.

Our review has limitations, as any literature review is not without constraints. First, with respect to GWAS, which will not be able to identify all genetic influences, and GWAS cannot explain 100% of the heritability of all traits. Second, we have excluded studies that reported the same genes and SNPs, and lastly, reviews with concurrent animal studies. Our review has several strengths as we undertook a systematic approach to screening and analyzing the GWASs from recent literature and secondly from the data presented, which can be utilized for clinical translation.

CONCLUSION

The goal of the HGP was to decipher the chemical sequence of the complete human genetic material, which ultimately can predict human diseases before they occur. The GWASs on osteoporosis have unfolded genetic influence and identified genes and SNPs that reduce BMD cause osteoporosis and inflict fragility fractures. Genetic analysis can now identify at-risk individuals with impending osteoporosis and fragility fractures so that they can change their lifestyle by practicing weight-bearing exercise, improving nutrition, and reducing smoking.

The analysis showed that 150 genes and 515 loci that target BMD and 15 loci, which increasefracture risk in osteoporosis, have been identified. Based on this review, it can be emphasized that there is a strong genetic influence on the attainment of BMD and increased risk of fragility fractures.

RECOMMENDATION

It is strongly recommended that we conduct GWASs on osteoporosis in the Saudi Arabian population to identify the genetic risk so that we can advise at-risk individuals to change their lifestyle so that they can limit the complications of osteoporosis and related complications.

AUTHORS' CONTRIBUTIONS

MSA conceived and designed the study, conducted review of literature, wrote the preliminary, manuscript, and complete the final manuscript. RAI performed the review of literature, completed the data analysis and manuscript review. HA helped in the data analysis, cross-checking of the references, and review of the final manuscript, and MA performed the final check of the analyzed data, review of literature, and final review of manuscript. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

ETHICAL APPROVAL

The Institutional Review Board approval is not required.

DECLARATION OF PATIENT CONSENT

Patient's consent not required as patients identity is not disclosed or compromised.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY FOR MANUSCRIPT PREPARATION

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

CONFLICTS OF INTEREST

All authors declare that they do not have any conflict of interest related to the submitted work.

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REFERENCES

1. Pouresmaeili F, Kamalidehghan B, Kamarehei M, Goh YM. A comprehensive overview on osteoporosis and its risk factors. Ther Clin Risk Manag 2018;14:2029-49.
2. Zhu X, Zheng H. Factors influencing peak bone mass gain. Front Med 2021;15:53-69.
3. Liu ZH, Zhao YL, Ding GZ, Zhou Y. Epidemiology of primary osteoporosis in China. Osteoporos Int 1997;Suppl 3:S84-7.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007;22:465-75.
5. Cooper C, Campion G, Melton LJ 3rd. Hip fractures in the elderly: A worldwide projection. Osteoporos Int 1992;2:285-9.
6. Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of osteoporosis-related fractures and costs in China: 2010-2050. Osteoporos Int 2015;26:1929-37.
7. Peacock M, Turner CH, Econs MJ, Foroud T. Genetics of osteoporosis. Endocr Rev 2002;23:303-26.
8. Zheng HF, Spector TD, Richards JB. Insights into the genetics of osteoporosis from recent genome-wide association studies. Expert Rev Mol Med 2011;13:e28.
9. Trajanoska K, Rivadeneira F. The genetic architecture of osteoporosis and fracture risk. Bone 2019;126:2-10.
10. Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: Advances and challenges. Nat Rev Genet 2012;13:576-88.
11. Styrkarsdottir U, Thorleifsson G, Sulem P, Gudbjartsson DF, Sigurdsson A, Jonasdottir A, *et al*. Nonsense mutation in the LGR4 gene is associated with several human diseases and other traits. Nature 2013;497:517-20.
12. Zheng HF, Forgetta V, Hsu YH, Estrada K, Rosello-DiezA, Leo PJ, *et al*. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature 2015;526:112-7.
13. Larsson SC, Michaëlsson K, Burgess S. Mendelian randomization in the bone field. Bone 2019;126:51-8.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
15. Kiel DP, Demissie S, Dupuis J, Lunetta KL, Murabito JM, Karasik D. Genome-wide association with bone mass and geometry in the Framingham Heart Study. BMC Med Genet 2007;8(Suppl 1):S14.
16. Xiong DH, Liu XG, Guo YF, Tan LJ, Wang L, Sha BY, *et al*. Genome-wide association and follow-up replication studies identified ADAMTS18 and TGFBR3 as bone mass candidate genes in different ethnic groups. Am J Hum Genet 2009;84:388-98.
17. Liu YZ, Pei YF, Liu JF, Yang F, Guo Y, Zhang L, *et al*. Powerful bivariate genome-wide association analyses suggest the SOX6 gene influencing both obesity and osteoporosis phenotypes in males. PLoS One 2009;4:e6827.
18. Rivadeneira F, Styrkársdottir U, Estrada K, Halldórsson BV, Hsu YH, Richards JB, *et al*. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. Nat Genet 2009;41:1199-206.
19. Guo Y, Tan LJ, Lei SF, Yang TL, Chen XD, Zhang F, *et al*. Genome-wide association study identifies ALDH7A1 as a novel susceptibility gene for osteoporosis. PLoS Genet 2010;6:e1000806.
20. Guo Y, Zhang LS, Yang TL, Tian Q, Xiong DH, Pei YF, *et al*. IL21R and PTH may underlie variation of femoral neck bone mineral density as revealed by a genome-wide association study. J Bone Miner Res 2010;25:1042-8.
21. Hsu YH, Zillikens MC, Wilson SG, Farber CR, Demissie S, Soranzo N, *et al*. An integration of genome-wide association study and gene expression profiling to prioritize the discovery of novel susceptibility Loci for osteoporosis-related traits. PLoS Genet 2010;6:e1000977.
22. Tan L, Liu R, Lei S, Pan R, Yang T, Yan H, *et al*. A genome-wide association analysis implicates SOX6 as a candidate gene for wrist bone mass. Sci China Life Sci 2010;53:1065-72.
23. Paternoster L, Ohlsson C, Sayers A, Vandenput L, Lorentzon M, Evans DM, *et al*. OPG and RANK polymorphisms are both associated with cortical bone mineral density: Findings from a meta-analysis of the Avon longitudinal study of parents and children and gothenburg osteoporosis and obesity determinants cohorts. J Clin Endocrinol Metab 2010;95:3940-8.
24. Kou I, Takahashi A, Urano T, Fukui N, Ito H, Ozaki K, *et al*. Common variants in a novel gene, FONG on chromosome 2q33.1 confer risk of osteoporosis in Japanese. PLoS One 2011;6:e19641.
25. Duncan EL, Danoy P, Kemp JP, Leo PJ, McCloskey E, Nicholson GC, *et al*. Genome-wide association study using extreme truncate selection identifies novel genes affecting bone mineral density and fracture risk. PLoS Genet 2011;7:e1001372.
26. Lei SF, Shen H, Yang TL, Guo Y, Dong SS, Xu XH, *et al*. Genome-wide association study identifies HMGN3 locus for spine bone size variation in Chinese. Hum Genet 2012;131:463-9.
27. Liu CT, Estrada K, Yerges-Armstrong LM, Amin N,

Evangelou E, Li G, *et al*. Assessment of gene-by-sex interaction effect on bone mineral density. J Bone Miner Res 2012;27:2051-64.
28. Guo YF, Zhang LS, Liu YJ, Hu HG, Li J, Tian Q, *et al*. Suggestion of GLYAT gene underlying variation of bone size and body lean mass as revealed by a bivariate genome-wide association study. Hum Genet 2013;132:189-99.
29. Deng FY, Dong SS, Xu XH, Liu YJ, Liu YZ, Shen H, *et al*. Genome-wide association study identified UQCC locus for spine bone size in humans. Bone 2013;53:129-33.
30. Zhang L, Choi HJ, Estrada K, Leo PJ, Li J, Pei YF, *et al*. Multistage genome-wide association meta-analyses identified two new loci for bone mineral density. Hum Mol Genet 2014;23:1923-33.
31. Tan LJ, Wang ZE, Wu KH, Chen XD, Zhu H, Lu S, *et al*. Bivariate genome-wide association study implicates ATP6V1G1 as a novel pleiotropic locus underlying osteoporosis and age at menarche. J Clin Endocrinol Metab 2015;100:E1457-66.
32. Mullin BH, Walsh JP, Zheng HF, Brown SJ, Surdulescu GL, Curtis C, *et al*. Genome-wide association study using family-based cohorts identifies the WLS and CCDC170/ESR1 loci as associated with bone mineral density. BMC Genomics 2016;17:136.
33. Hwang JY, Kim YJ, Choi BY, Kim BJ, Han BG. Meta analysis identifies a novel susceptibility locus associated with heel bone strength in the Korean population. Bone 2016;84:47-51.
34. Choi HJ, Park H, Zhang L, Kim JH, Kim YA, Yang JY, *et al*. Genome-wide association study in East Asians suggests UHMK1 as a novel bone mineral density susceptibility gene. Bone 2016;91:113-21.
35. Pei YF, Hu WZ, Hai R, Wang XY, Ran S, Lin Y, *et al*. Genome-wide association meta-analyses identified 1q43 and 2q32.2 for hip Ward's triangle areal bone mineral density. Bone 2016;91:1-10.
36. Pei YF, Xie ZG, Wang XY, Hu WZ, Li LB, Ran S, *et al*. Association of 3q13.32 variants with hip trochanter and intertrochanter bone mineral density identified by a genome-wide association study. Osteoporos Int 2016;27:3343-54.
37. Mullin BH, Zhao JH, Brown SJ, Perry JRB, Luan J, Zheng HF, *et al*. Genome-wide association study meta-analysis for quantitative ultrasound parameters of bone identifies five novel loci for broadband ultrasound attenuation. Hum Mol Genet 2017;26:2791-802.
38. Villalobos-Comparán M, Jiménez-Ortega RF, Estrada K, Parra-Torres AY, González-Mercado A, Patiño N, *et al*. A Pilot genome-wide association study in postmenopausal Mexican-Mestizo women implicates the RMND1/CCDC170 locus is associated with bone mineral density. Int J Genomics 2017;2017:5831020.
39. Kemp JP, Morris JA, Medina-Gomez C, Forgetta V, Warrington NM, Youlten SE, *et al*. Identification of 153 new loci associated with heel bone mineral density and functional involvement of GPC6 in osteoporosis. Nat Genet 2017;49:1468-75.
40. Peng C, Lou HL, Liu F, Shen J, Lin X, Zeng CP, *et al*. Enhanced identification of potential pleiotropic genetic variants for bone mineral density and breast cancer. Calcif Tissue Int 2017;101:489-500.
41. Lu S, Zhao LJ, Chen XD, Papasian CJ, Wu KH, Tan LJ, *et al*. Bivariate genome-wide association analyses identified genetic pleiotropic effects for bone mineral density and alcohol drinking in Caucasians. J Bone Miner Metab 2017;35:649-58.
42. Pei YF, Hu WZ, Yan MW, Li CW, Liu L, Yang XL, *et al*. Joint study of two genome-wide association meta-analyses identified 20p12.1 and 20q13.33 for bone mineral density. Bone 2018;110:378-85.
43. Lin X, Peng C, Greenbaum J, Li ZF, Wu KH, Ao ZX, *et al*. Identifying potentially common genes between dyslipidemia and osteoporosis using novel analytical approaches. Mol Genet Genomics 2018;293:711-23.
44. Qiu C, Shen H, Fu X, Xu C, Deng H. Meta-analysis of genome-wide association studies identifies novel functional CpG-SNPs associated with bone mineral density at lumbar spine. Int J Genomics 2018;2018:6407257.
45. Gregson CL, Newell F, Leo PJ, Clark GR, Paternoster L, Marshall M, *et al*. Genome-wide association study of extreme high bone mass: Contribution of common genetic variation to extreme BMD phenotypes and potential novel BMD-associated genes. Bone 2018;114:62-71.
46. Naito T, Yokoyama N, Kakuta Y, Ueno K, Kawai Y, Onodera M, *et al*. Clinical and genetic risk factors for decreased bone mineral density in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol 2018;33:1873-81.
47. Liang X, Wu C, Zhao H, Liu L, Du Y, Li P, *et al*. Assessing the genetic correlations between early growth parameters and bone mineral density: A polygenic risk score analysis. Bone 2018;116:301-6.
48. Styrkarsdottir U, Stefansson OA, Gunnarsdottir K, Thorleifsson G, Lund SH, Stefansdottir L, *et al*. GWAS of bone size yields twelve loci that also affect height, BMD, osteoarthritis or fractures. Nat Commun 2019;10:2054.
49. Zhang H, Liu L, Ni JJ, Wei XT, Feng GJ, Yang XL, *et al*. Pleiotropic loci underlying bone mineral density and bone size identified by a bivariate genome-wide association analysis. Osteoporos Int 2020;31:1691-701.
50. Richards JB, Rivadeneira F, Inouye M, Pastinen TM, Soranzo N, Wilson SG, *et al*. Bone mineral density, osteoporosis, and osteoporotic fractures: A genome-wide association study. Lancet 2008;371:1505-12.
51. Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, Gudbjartsson DF, Walters GB, Ingvarsson T, *et al*. Multiple genetic loci for bone mineral density and fractures. N Engl J Med 2008;358:2355-65.
52. Kung AW, Xiao SM, Cherny S, Li GH, Gao Y, Tso G, *et al*. Association of JAG1 with bone mineral density and osteoporotic fractures: A genome-wide association study and follow-up replication studies. Am J Hum Genet 2010;86:229-39.
53. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, *et al*. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet 2012;44:491-501.
54. Zheng HF, Tobias JH, Duncan E, Evans DM, Eriksson J, Paternoster L, *et al*. WNT16 influences bone mineral density, cortical bone thickness, bone strength, and osteoporotic fracture risk. PLoS Genet 2012;8:e1002745.
55. Hwang JY, Lee SH, Go MJ, Kim BJ, Kou I, Ikegawa S, *et al*. Meta-analysis identifies a MECOM gene as a novel predisposing factor of osteoporotic fracture. J Med Genet 2013;50:212-9.
56. Zheng HF, Duncan EL, Yerges-Armstrong LM, Eriksson J,

Bergström U, Leo PJ, *et al*. Meta-analysis of genome-wide studies identifies MEF2C SNPs associated with bone mineral density at forearm. J Med Genet 2013;50:473-8.
57. Taylor KC, Evans DS, Edwards DRV, Edwards TL, Sofer T, Li G, *et al*. A genome-wide association study meta-analysis of clinical fracture in 10,012 African American women. Bone Rep 2016;5:233-42.
58. Styrkarsdottir U, Thorleifsson G, Gudjonsson SA, Sigurdsson A, Center JR, Lee SH, *et al*. Sequence variants in the PTCH1 gene associate with spine bone mineral density and osteoporotic fractures. Nat Commun 2016;7:10129.
59. Styrkarsdottir U, Thorleifsson G, Eiriksdottir B, Gudjonsson SA, Ingvarsson T, Center JR, *et al*. Two rare mutations in the COL1A2 gene associate with low bone mineral density and fractures in Iceland. J Bone Miner Res 2016;31:173-9.
60. Kim SK. Identification of 613 new loci associated with heel bone mineral density and a polygenic risk score for bone mineral density, osteoporosis and fracture. PLoS One 2018;13:e0200785.
61. Trajanoska K, Morris JA, Oei L, Zheng HF, Evans DM, Kiel DP, *et al*. Assessment of the genetic and clinical determinants of fracture risk: Genome wide association and mendelian randomisation study. BMJ 2018;362:k3225.
62. Alonso N, Estrada K, Albagha OME, Herrera L, Reppe S, Olstad OK, *et al*. Identification of a novel locus on chromosome 2q13, which predisposes to clinical vertebral fractures independently of bone density. Ann Rheum Dis 2018;77:378-85.
63. Morris JA, Kemp JP, Youlten SE, Laurent L, Logan JG, Chai RC, *et al*. An atlas of genetic influences on osteoporosis in humans and mice. Nat Genet 2019;51:258-66.
64. Tang PL, Cheung CL, Sham PC, McClurg P, Lee B, Chan SY, *et al*. Genome-wide haplotype association mapping in mice identifies a genetic variant in CER1 associated with BMD and fracture in southern Chinese women. J Bone Miner Res 2009;24:1013-21.
65. Koller DL, Ichikawa S, Lai D, Padgett LR, Doheny KF, Pugh E, *et al*. Genome-wide association study of bone mineral density in premenopausal European-American women and replication in African-American women. J Clin Endocrinol Metab 2010;95:1802-9.
66. Koller DL, Zheng HF, Karasik D, Yerges-Armstrong L, Liu CT, McGuigan F, *et al*. Meta-analysis of genome-wide studies identifies WNT16 and ESR1 SNPs associated with bone mineral density in premenopausal women. J Bone Miner Res 2013;28:547-58.
67. Timpson NJ, Sayers A, Davey-Smith G, Tobias JH. How does body fat influence bone mass in childhood? A Mendelian randomization approach. J Bone Miner Res 2009;24:522-33.
68. Medina-Gomez C, Kemp JP, Estrada K, Eriksson J, Liu J, Reppe S, *et al*. Meta-analysis of genome-wide scans for total body BMD in children and adults reveals allelic heterogeneity and age-specific effects at the WNT16 locus. PLoS Genet 2012;8:e1002718.
69. Chesi A, Mitchell JA, Kalkwarf HJ, Bradfield JP, Lappe JM, McCormack SE, *et al*. A trans-ethnic genome-wide association study identifies gender-specific loci influencing pediatric aBMD and BMC at the distal radius. Hum Mol Genet 2015;24:5053-9.
70. Ralston SH, Uitterlinden AG. Genetics of osteoporosis. Endocr Rev 2010;31:629-62.
71. Rivadeneira F, Mäkitie O. Osteoporosis and bone mass disorders: From gene pathways to treatments. Trends Endocrinol Metab 2016;27:262-81.
72. Stewart TL, Ralston SH. Role of genetic factors in the pathogenesis of osteoporosis. J Endocrinol 2000;166:235-45.
73. Van Meurs JB, Trikalinos TA, Ralston SH, Balcells S, Brandi ML, Brixen K, *et al*. Large-scale analysis of association between LRP5 and LRP6 variants and osteoporosis. JAMA 2008;299:1277-90.
74. Zmuda JM. Identification of osteoporosis risk genes: The tip of the iceberg. Ann Intern Med 2009;151:581-2.
75. Boudin E, Steenackers E, de Freitas F, Nielsen TL, Andersen M, Brixen K, *et al*. A common LRP4 haplotype is associated with bone mineral density and hip geometry in men-data from the Odense Androgen Study (OAS). Bone 2013;53:414-20.
76. Richards JB, Kavvoura FK, Rivadeneira F, Styrkársdóttir U, Estrada K, Halldórsson BV, *et al*. Collaborative meta-analysis: Associations of 150 candidate genes with osteoporosis and osteoporotic fracture. Ann Intern Med 2009;151:528-37.
77. Zhu X, Bai W, Zheng H. Twelve years of GWAS discoveries for osteoporosis and related traits: Advances, challenges and applications. Bone Res 2021;9:23.
78. Sadat-Ali M, Al-Habdan IM, Al-Turki HA, Azam MQ. An epidemiological analysis of the incidence of osteoporosis and osteoporosis-related fractures among the Saudi Arabian population. Ann Saudi Med 2012;32:637-41.
79. Sadat-Ali M, Al-Dakheel DA, Azam MQ, Al-Bluwi MT, Al-Farhan MF, AlAmer HA, *et al*. Reassessment of osteoporosis-related femoral fractures and economic burden in Saudi Arabia. Arch Osteoporos 2015;10:37.
80. Sadat-Ali M, Al-Turki HA. Genetic influence of candidate osteoporosis genes in Saudi Arabian population: A pilot study. J Osteoporos 2012;2012:569145.