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Chapter 3

Genetic Disorders Associated with Osteoporosis

Shishu Huang, Gordon Cheung-Toa Ng and Song You-Qiang

Additional information is available at the end of the chapter

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1. Introduction

Osteoporosis (OP) is a common skeletal disease and a global problem. The prevalence of OP is approximately 10.3% in the general population and affects over 200 million women worldwide [1]. Approximately 30% of postmenopausal women suffer from OP in Western nations. About 50% of affected women and at least 15% of affected men will undergo fragility fractures in their lifetime. OP is chronic and does not present with apparent symptoms before osteoporostic fractures occur. This can cause disability, a decreased quality of life, and even death. As a result, OP imposes a heavy financial burden on society that includes not only the direct cost of osteoporostic fractures but also the indirect costs of disablement. In the United States, the direct cost of OP was over USD 13.7 billion in 2005 and may reach USD 25.3 billion by 2025. Therefore, OP is a pressing public health concern and greater understanding of its mechanisms is imperative.

Population ageing is accelerating worldwide, and OP is becoming increasingly prevalent. However, the risk factors that contribute to OP are not clear. Many factors have been suggested to affect the likelihood of OP, including genetics, gender, age, poor diet, smoking and medications (Figure 1). It has been reported that the genetic heritability of bone loss in humans is up to 56% [2,3]. This has been found through comparisons of bone mineral density (BMD), the hallmark trait of OP, in monozygotic (MZ) and dizygotic (DZ) twins after menopause. Additionally, a genome-wide association study (GWAS) of 37,534 individuals in Europe and North America has confirmed that LRP5 (lipoprotein-receptor-related protein) significantly increases the risk of OP and osteoporotic fractures [4]. Therefore, genetic factors play a significant role in the aetiology of OP and its complications.

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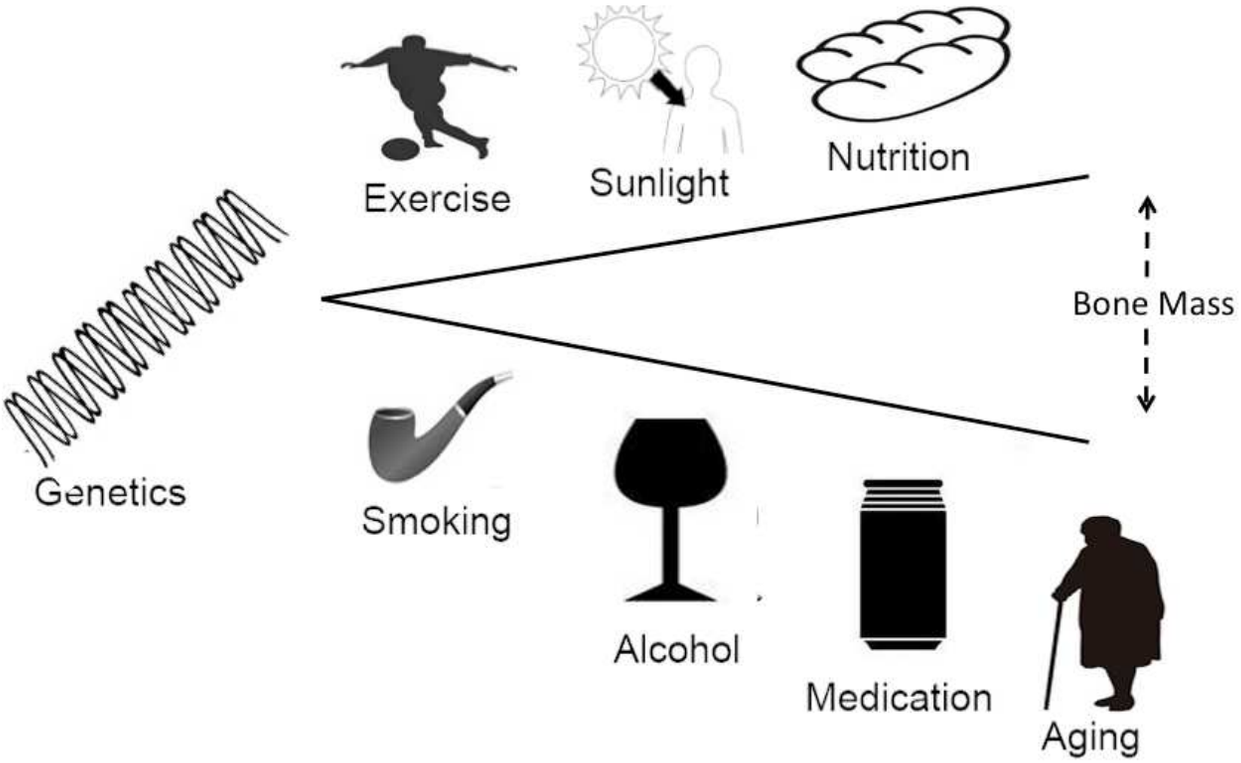


Figure 1. Bone mass is affected by genetic (60%~80% contribution) and other factors (20%~40% contribution) including exercise, sunlight, nutrition, smoking, alcohol, medication and ageing. Factors along the upline potentially contribute to higher bone mass and along the downline cause lower bone mass.

OP is characterized by reduced BMD, impaired microarchitecture of bone tissue and increased risk of fractures. OP has a wide range of phenotypes including abnormal BMD, bone turnover, osteoporotic fracture, skeletal growth, and fracture risk. Although OP genetics aims to identify pathological genes that increase the chance of bone fragility, osteoporotic fractures are not appropriate candidate phenotypes for heritability studies. As fractures occur due to a wide variety of reasons, not necessarily as a result of bone fragility, fractures alone are insufficient qualifiers for studies. In contrast, previous studies have reported a strong genetic correlation between BMD and bone mass/fracture phenotypes [5]. To this date, most OP studies have focused on BMD because of the high heritability and relative ease of measurement. This chapter will discuss the hereditary factors in pursuit of a new understanding of pathological genes in OP, including an overview of current technology at the cutting-edge of OP testing.

2. Non-genetic factors in the risk of osteoporosis

OP may be caused by primary and secondary factors (Table 1). Mostly, OP results from primary factors; in approximately 20%~40% of patients the condition has secondary causes [5,6]. Primary OP has two categories: type I (postmenopausal) and type II (senile) OP. Type I OP is believed to be associated with oestrogen deficiency and usually occurs in women between the ages of 51 and 75. It results in excessive bone resorption and fractures, including in the

trabecular bone in the vertebrae and distal radius. Type II OP usually results from age-related vitamin D deficiency and affects women and men over the age of 70. It mainly causes hypocalcaemia, increased parathyroid hormone (PTH) release, bone resorption and fractures, including in both the trabecular and cortical bone on the long bones, causing fractures of the femoral neck, proximal, humerus and tibia, and pelvis.

Identifiable Causes	
Primary cause	***Secondary cause***
Personal condition	Chronic glucocorticoid therapy
Oestrogen deficiency	Thyrotoxicosis
Low weight and body mass index	Vitamin D deficiency
Increased age	Alcoholism and smoking
Gender	Hypogonadism (men)
Family history	Malnutrition

Table 1. Identifiable causes of osteoporosis

As discussed in detail in other chapters of this book, OP is a chronic and complex disease that is influenced by both non-genetic and genetic factors. Non-genetic factors are common and worthy of consideration (Table 2). One of the most important is oestrogen, which changes with age [6, 7]. Oestrogen acts directly on oestrogen receptors in osteoblasts and its deficiency affects BMD, which leads to the risk of OP in postmenopausal women and contributes to the development of OP in elderly men. The chemical element lead is another potential risk factor for OP. Lead impairs cell proliferation and viability by affecting the response of cells to hormonal stimuli, which interferes with hormone and cytokine signal-transduction processes. This causes a toxic effect in skeleton systems and influences bone mineral homeostasis and growth. Calcium is one of our most common body minerals and is required for normal skeletal growth and maintenance [8]. A low-calcium diet causes loss of trabecular bone by affecting the function and phenotype of bone-marrow cells [8-10]. This has been shown to further accelerate bone loss in ovariectomized (OVX) rats, though BMD levels were partially rescued by calcium supplements [8-10]. Cadmium is toxic and causes bone loss after the start of dietary cadmium exposure [11-12]. It has been demonstrated that cadmium exposure leads to an increase in serum calcium, phosphorous and PTH levels in concomitant with significant reduction in serum vitamin D (3), osteocalcin (OC) levels and bone-specific alkaline phosphatase (BALP) activity [11-12]. Reduced BMD is usually associated with kidney impairment in response to cadmium exposure [12]. Although the toxic effects of aluminium overload on bone metabolism were first reported with a severe form of osteomalacic osteodystrophy [13], recently it has been reported that accumulated aluminium content in bone during life does not substantially

influence the level of BMD [14-15]. Additionally, no clinical symptoms of bone disease were found in individuals with aluminium contamination, but its accumulation in tissue was significant [14-15]. Interestingly, dual X-ray absorptiometry (DXA) was found to induce BMD recovery in osteopenic rats affected by aluminium [16]. Alcohol slows cell proliferation and viability to arrest longitudinal bone growth, and affects dry weight, mineral content and mechanical integrity [17-18]. This may increase the risk of developing OP – further confirmation is given by epidemiological findings. Additionally, studies on animals have reported that alcohol suppresses young bone growth and inhibits adult bone formation – alcohol has greater deleterious effects on bone formation than on bone resorption [18]. Smoking, particularly heavy smoking, may affect nutritional absorption, decrease absorption of calcium, and interfere with oestrogen. This eventually results in lower oestrogen levels, lower bone density, a dramatic decrease in the bone mass/mineralization, and a higher incidence of bone fractures [19-21]. Notably, smoking duration was not associated with BMD in 1,054 subjects, including 26.2% of current smokers (n=276), 17.7% of former smokers (n=187), and 56.1% of never smokers (n=591) [21].

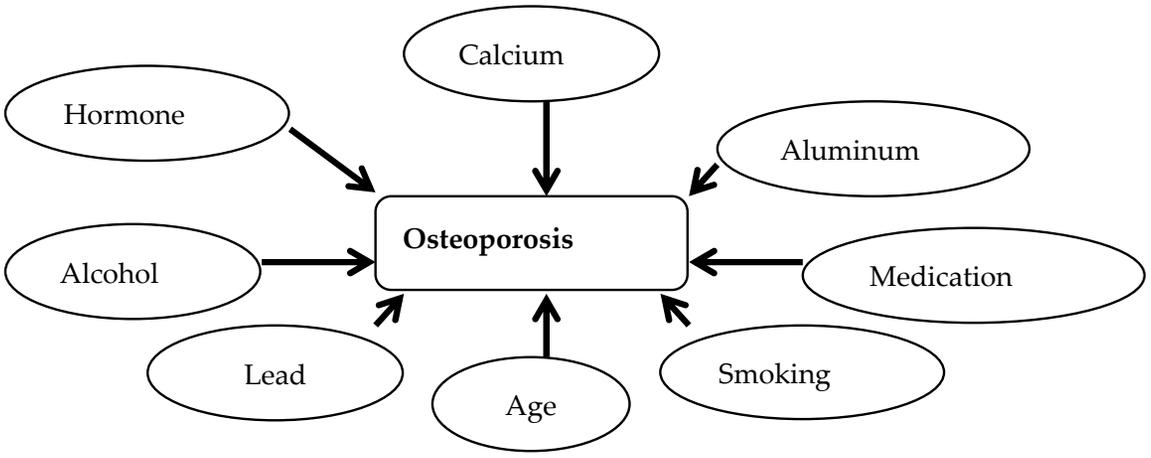


Table 2. Non-genetic factors in the risk of osteoporosis.

Although non-genetic factors play a significant role in determination of the risk of OP, twin and family studies have reported that up to 60~80% of the variance in BMD is attributable to genetic factors. Non-genetic factors vary markedly among individuals who show different bone response to stimuli, and genetic factors appear to be more dominant than the combination of non-genetic factors in the pathogenesis of OP. The search for pathogenic genes that cause OP remains one of the greatest challenges and the most active scientific area in musculoskeletal research. Despite the impact of environmental factors, it has been confirmed that genes related to OP exist and have pathogenicity. These are multiple genes with small individual effects; not more than 10% are associated with BMD. Therefore, the impact of genetic factors in the pathogenesis of OP is still unclear. To date, different methods have been used to identify the susceptible genes related to OP (Fig. 2.). These are elaborated below.

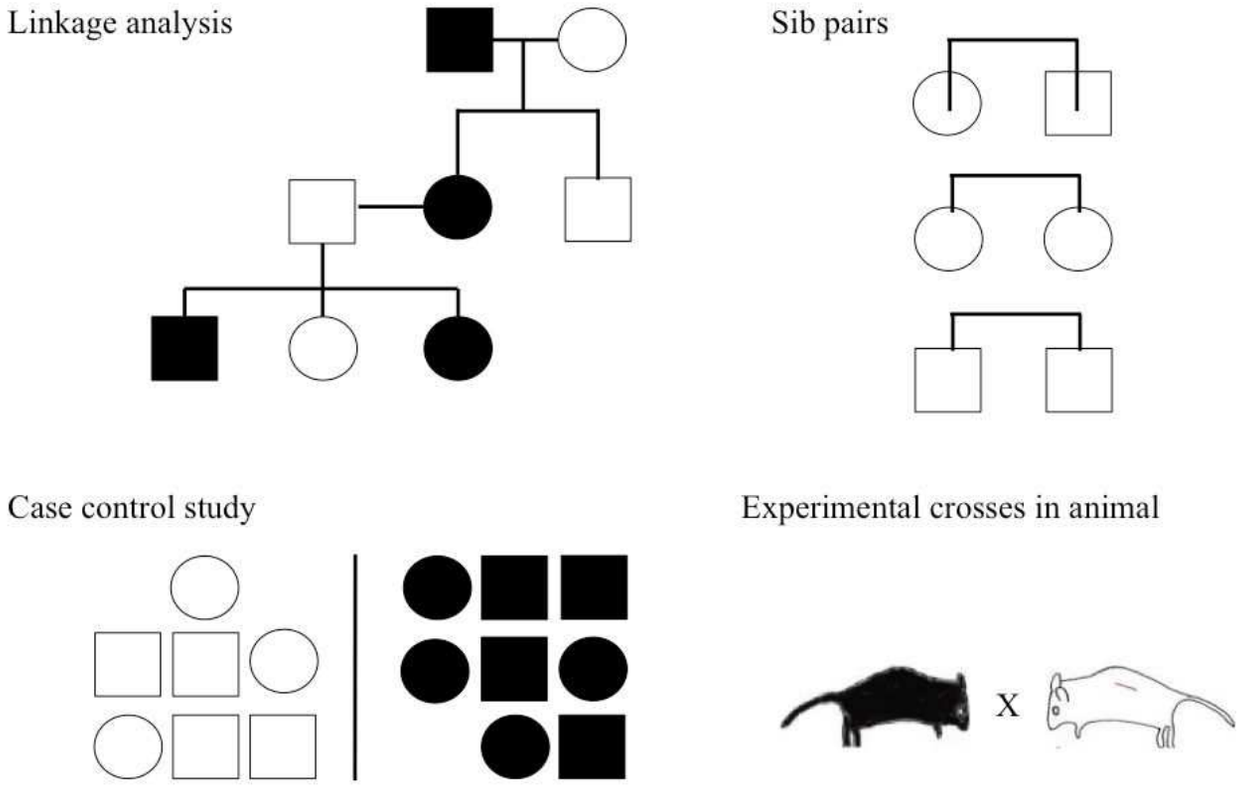


Figure 2. Strategies in the identification of genetic variants of osteoporosis and other complex diseases. Linkage studies in families and sibling pairs refer to phenotyping members of extended families for the feature of interest (e.g., BMD). The control study looks for the association of a marker allele with disease by comparison among unrelated subjects. Experimental crosses in animals are performed to prove the findings from linkage and candidate gene studies.

3. Genes associated with BMD in monogenic skeletal diseases

Ever since Mendel first elucidated the concept of inheritance in the pea plant, genetic analyses have used families, which often share similar genes, to study gene characteristics. With the development of genomic technology, the discovery of genetic markers spanning the entire human genome for Mendelian diseases and traits has been achieved after widespread mapping efforts. Major monogenic skeletal disorders with OP that have been identified to date include osteogenesis imperfecta, Bruck syndrome, osteopetrosis, high-bone-mass syndrome, osteoporosis-pseudoglioma syndrome, von Buchem disease, sclerosteosteosis, familial expansile osteolysis, juvenile Paget's disease, hypophosphatasia, neonatal hyperparathyroidism and pyknodysostosis. These diseases affect BMD and can cause either high- or low-mass syndrome.

Although many pathogenic genes have been identified (Table 3), many do not qualify as osteoporosis genes due to a lack of robustness. Low-density lipoprotein receptor-related 5 (LRP5) protein is a transmembrane low-density lipoprotein receptor which functions in receptor-mediated endocytosis [22-24]. The LRP5 gene was identified as the cause of the monogenic disease osteoporosis-pseudoglioma by mapping and candidate gene screening

[22-24]. Inactivation of LRP5 leads to the suppression of mechano-responsiveness and reduces bone mass and Young's modulus in osteoporosis-pseudoglioma [25, 26]. Activation of LRP5 increases bone mass in osteosarcoma. Furthermore, population-based and cohort studies have confirmed the significant association of LRP5 with BMD in Asian and European populations [27-29]. Bone fragility and risk of fracture have been reported with the mutation of LRP5 in families of affected patients. Patients with multiple thoracic vertebral fractures were confirmed to have about two compound heterozygous missense mutations in LRP5 [30, 31]. Meta-analyses and genome-wide studies carried out for separate large populations have revealed consistency between LRP5 variants in BMD and fracture risk – this will be further addressed in the next part. In addition to LRP5, low-density lipoprotein-related 4 (LRP4) protein was identified as a candidate sclerostin interaction partner by an unbiased proteomics approach [32]. The mutation of LRP4 has been reported to be associated with bone overgrowth by impairing the sclerostin facilitator function.

AR	AHSG	ApoE	BMP2	BGP	CASR
CLCN7	COL1A1	COL1A2	CT	CYR1B1	COMT
CYP1A1	CYP17	CTR	CYP19	CCR2	DBP
DRD4	ERbeta	ERalpha	FRA-1	GH1	GnRH
HLA-A	IL-6	LRP5	LRP4	LCT	IL-1RA
LEPR	IL-10	I-TRAF	IRAK1	IGF-1	IGF-II
Klotho	MMP-1	MGP	MTHFR	MMP-9	NPY
NCOA3	OSCAR	OPG	P57(KIP2)	PON1	PDE4
PPARG	PLDO1	PTHR1	PTH	PDE4D	QPCT
RIL	RUNX2	Sox4	SERT	SOST	TNFalpha
TNFR2	TCIRG1	TGFbeta	WRN		

Table 3. Genes associated with BMD/osteoporosis. These genes are identified through association studies and correlate with BMD and osteoporosis-related phenotype.

Vitamin D receptor (VDR) is one of the trans-acting transcriptional regulatory factors that regulate proteins involved in bone mineral homeostasis. It has been reported that the polymorphism of the third region of VDR is significantly associated with BMD, and the allelic variation of this gene may contribute 75% of the genetic effect on BMD change [33]. Additionally, the polymorphism of the VDR gene, including Bsml, Apal, Fokl and Taq genotypes, regulates BMD and is associated with OP [34-37]. VDR polymorphisms emerge in the rheumatoid-related OP and the ApaI, BsmI and TaqI polymorphisms may be susceptible risk factors for rheumatoid arthritis (RA). Interestingly, the Ff genotype may be responsible for development of OP in RA [38, 39].

Type I collagen is a constituent major-bone protein, and the genes (COLIA1 and COLIA2) are believed to be candidates for genetic control of BMD. The COLIA1 gene polymorphism is

suggested to be implicated in reduced BMD and increased fracture incidence [40]. Mutations in the two genes for type I collagen have been confirmed to cause osteogenesis imperfecta, and are associated with OP in postmenopausal women [41, 42]. Population-based studies have indicated that COL1A1 Sp1 polymorphism may contribute to the development of OP such that Sp1 polymorphic variants of COL1A1 gene are associated with BMD values [43-46]. The "ss" and "TT" genotypes possess lower lumbar-spine BMD [46].

The oestrogen-receptor gene encodes an oestrogen receptor (ESR), a member of the super-family of nuclear receptors that are involved in DNA and hormone binding and activation of transcription. The ESR can interact with oestrogen and transcription factors including SP-1, AP-1 and NF-κB. As oestrogens are important endocrine regulators in skeletal growth and maintenance, oestrogen-deficient animals exhibit reduced BMD and oestrogen substitution shows restored bone compartments [47-49]. One case of OP in a male patient was reported to show an inactivating mutation of the ESR gene, which was parallel with the male knockout mice with null alleles at the ESR locus [50]. However, inactivation of ESR alpha, specifically in nervous tissue, the main ER for oestrogenic bone effects, causes increased BMD in mouse trabecular and cortical bone [51]. Interestingly, ER alpha in osteocytes has been shown to play an osteoprotective role in the trabecular bone formation, confirmed by tests on ER alpha-deletion mice [52].

Although many genes have been identified in monogenic skeletal disorders connected to OP, the linkage data have not been sufficiently robust due to sample size and significance. Studies in OP genetics need to facilitate more powerful and more sophisticated approaches, such as GWAS studies, to achieve the identification of OP heritable factors.

4. Genome-wide association study and BMD

Genome-wide association study (GWAS) aims to identify disease-associated loci called single nucleotide polymorphisms (SNPs), which contribute to small variations of BMD in the genome. If an allele of an SNP occurs significantly more or less frequently in people with a particular disease than in people without the disease, the allele is associated with the disease traits. Although previous linkage and candidate-gene studies have provided few replicated loci for OP, genome-wide association approaches have produced clear and reproducible findings.

Two SNPs, rs3736228 on chromosome 11 in the LRP5 gene and rs4355801 on chromosome 8 near the TNFRSF11B gene, were reported to cause risk of OP and osteoporotic fracture in 2,094 British women [53]. The rs3736228 in the LRP5 gene was identified to correlate with decreased BMD in lumbar spine and femoral neck. The rs4355801 near the TNFRSF11B gene correlated with decreased BMD for lumbar spine and femoral neck [53]. In a study of 583 postmenopausal women, the polymorphism of three variants TNFRSF11B (rs4355801, rs2073618, and rs6993813) and one of LRP5 (rs3736228) was further confirmed to be associated with BMD variations [54]. In a prospective study of 37,534 subjects in Europe and North America, variants of LRP5 (rs3736228, rs4988321) and one variant of LRP6 (rs2302685) were examined in terms

of their effect on BMD and contribution to risk of fracture. The rs3736228 and rs4988321 variants of LRP5 were associated with reduced lumbar-spine BMD, femoral-neck BMD, and fractures. The rs2302685 of LRP6 polymorphism was not associated with any OP phenotype, including reduced BMD and fracture [55, 56]. This was further confirmed in a study of 944 postmenopausal Spanish women, where the rs2302685 variant of the LRP6 polymorphism was not significantly associated with lumbar-spine or femoral-neck BMD [57]. LRP4 was also analysed for SNP in cohort studies of European populations. One associated SNP of LRP4 (rs6485702) was significant in hip and whole-body BMD, modulated through the Wnt and BMP signalling pathways [58, 59].

Other gene polymorphisms associated with changes in BMD included the Cerberus 1 (CER1) gene, ADAM metallopeptidase with thrombospondin type 1 motif 18 (ADAMTS18), transforming growth factor beta receptor III (TGFBR3), high-mobility group (HMG), signal transducer and activator of transcription 1 (STAT1), aldehyde dehydrogenase (ALDH), PTH, and sperm-ion channel gene CatSper channel auxiliary subunit beta (CATSPERB). In a cohort of 1,083 human subjects, one SNP (rs3747532) in human CER1 gene was reported to play a role in the increased risk of low BMD in women prior to menopause and a vertebral fractures cohort [60]. In an association test of 379,319 SNPs in 1,000 unrelated American white individuals, ADAMTS18 and TGFBR3 were reported as BMD candidate genes in meta-analyses [61]. Additionally, individuals with normal skeletal fractures were different to individuals with non-union skeletal fracture in the expression of both genes [61]. In two cohorts of 1,548 Caucasian American men and 1,680 Afro-Caribbean men, the rs1042725 of the HMGA2 polymorphism was reported to be associated with decreased tibia trabecular volumetric BMD [62]. In a GWAS of 1,000 unrelated Caucasians, the STAT1 gene was significantly associated with BMD variation and was upregulated in the low BMD group rather than the high BMD group variation [63]. In a study of 700 elderly Chinese Han individuals (350 with hip osteoporotic fracture and 350 healthy controls), one SNP, rs13182402, within the ALDH7A1 gene on chromosome 5q31, was significantly associated with osteoporotic fractures [64]. This was further examined in relation to the relevance of hip BMD in Caucasian and Chinese populations (n=9,962), finding a consistent association with hip BMD [64]. The Interleukin 21 receptor (IL21R) encodes a cytokine receptor for interleukin 21 that activates multiple downstream signalling molecules, including STAT1, STAT3, JAK1 and JAK3. In a GWAS of 983 unrelated white subjects, the polymorphisms of the PTH gene (rs9630182, rs2036417, and rs7125774) and the polymorphisms of the IL21R gene (rs7199138, rs8061992 and rs8057551) were associated with changed femoral-neck BMD [65]. The polymorphisms of CATSPERB (rs1298989, rs1285635) were reported to be associated with femoral-neck BMD in 1,524 European-American premenopausal women and 669 African-American premenopausal women [66]. In particular, the rs1285635 in the European-American women was consistent with that in the African-American women [66].

Furthermore, meta-analysis of GWAS has shown more candidate genes and BMD loci reaching genome-wide significance. A meta-analysis of 19,195 Northern European subjects from five GWAS revealed nine genes from 150 identified genes associated with changed BMD: TNFSF11, TNFRSF11A, TNFRSF11B, LRP4, LRP5, ESR1, SPP1, ITGA1, and SOST [67]. Additionally, 13

new BMD loci were identified and included: 1p31.3 (GPR177), 2p21 (SPTBN1), 3p22 (CTNNB1), 4q21.1 (MEPE), 5q14 (MEF2C), 7p14 (STARD3NL), 7q21.3 (FLJ42280), 11p11.2 (LRP4, ARHGAP1, F2), 11p14.1 (DCDC5), 11p15 (SOX6), 16q24 (FOXL1), 17q21 (HDAC5) and 17q12 (CRHR1) [68]. In a meta-analysis of 18,098 subjects from six European-descent populations and an Asian population, rs2273061 of the Jagged1 (JAG1) gene was identified to be associated with BMD for lumbar spine and for femoral neck. The JAG1 gene therefore becomes a new candidate gene in the regulation of BMD and a new risk factor for bone-fracture pathogenesis [69]. In a meta-analysis of GWAS based on 3,657 Caucasian men and 7,633 Caucasian women, two genes and three new loci were identified as associated with OP-related traits and BMD in women, including SOX6, GPR177 gene, 2q11.2 (TBC1D8), chromosome 1p13.2 and 18q11.2 (OSBPL1A) [70]. A meta-analysis of GWAS data from European and Chinese individuals identified further genes associated with changed BMD located at 1q21.3, 9q22, 9q33.2, 20p13, and 20q12. This significantly correlates with the development and functionality of muscle, skeleton and connective tissue [71]. In a meta-analysis of 17 GWAS based on 32,961 subjects of East-Asian and European ancestry, 32 new loci were associated with BMD at genome-wide significance and were localized in 1q24.3, 2p21, 2q13, 2q14.2, 3q13.2, 3q25.31, 4p16.3, 6p21.1, 6p22.3, 7q31.31, 7q31.31, 7q36.1, 8q13.3, 9q34.11, 10p11.23, 10q21.1, 10q22.3_1, 10q24.2, 11p14.1_1, 12p11.22, 12p13.33, 12q13.12, 12q23.3, 14q32.12, 16p13.11, 16p13.3_1, 16p13.3_2, 16q12.1, 17p13.3, 17q24.3, 18p11.21, 19q13.11 and Xp22.31 [72]. Moreover, in a meta-analysis of 27,061 individuals, two new loci were of genome-wide significance: 14q24.2 (rs227425, SMOC1) in the whole sample and 21q22.13 (rs170183, CLDN14) in the female-specific sample. These were also shown to be significant in the results of the GEnetic Factors for Osteoporosis Consortium (GEFOS, n = 32,960) [73].

Thus, GWAS has been successfully used in uncovering key genes or markers associated with OP in humans and animals. Although it has confirmed the existence of relevant SNPs associated with changed BMD and the risk of OP, GWAS still cannot be absolutely accurate in the prediction of OP.

5. Genome-wide copy-number variants study and BMD

The first large-scale genome-wide studies of copy-number variants (CNVs) in humans were performed about a decade ago, and CNVs now make a larger contribution to genome variations than SNPs [74, 75]. Recent studies have focused on CNVs that may modulate gene function and affect disease risk. CNVs are structural genetic variants in the genome that alter the number of copies of one or more sections of DNA. This corresponds to large regions of the genome with deletion or duplication on certain chromosomes, and results in phenotypic variation.

Although CNV has been reported to correlate with many complex human diseases, the contribution of CNV to OP has not been revealed yet. A Chinese study of 700 elderly patients, comprising 350 individuals with homogeneous hip osteoporostic fracture and 350 control individuals, reported that CNV 4q13.2 significantly correlated with osteoporostic fracture

(P<0.0002). Additionally, a variant of UGT2B17 in CNV 4q13.2 was further proven to correlate with hip osteoporostic fracture in both white (1000 individuals) and Chinese (689 individuals), with consistently significant results (P=0.0005-0.021) [76].

Another genome-wide study of 1,000 Caucasian individuals found that a CNV in VPS13B gene, encoding a potential transmembrane protein involved in vesicle-mediated transport, was significantly associated with hip, spine and femoral-neck BMD. Interestingly, individuals with two copies of the CNV in the genome exhibited a higher level of BMD in the hip, spine and femoral neck, compared with one-copy subjects [77].

Another genome-wide CNV study tested 5,178 subjects in a prospective cohort in the Netherlands. It identified 210 kb deletion located on chromosome 6p25.1 that correlated with the risk of fracture (P=0.0000869). This deletion has geographic specificity, not affecting the populations of Australia, Canada, Poland, Iceland, Denmark, or Sweden. It has been found and is prevalent in Ireland (0.06%), England (0.15%), USA (0.23%), Scotland (0.10%), and Spain (0.33%), with insufficient significance of fracture risk. However, the role of the 6p25.1 locus in the prediction of risk of bone fracture needs to be tested in a larger and more diverse population to confirm the findings [78].

A study on 2,286 Caucasian individuals, and replicated in 1,627 Chinese individuals, identified two CNVs (CNV2580 and CNV1191) that correlated with appendicular lean mass (ALM), the main component of skeletal muscle. CNV1191 resides in the gene encoding GTPase of the immunity-associated protein family (GIMAP1), and is significantly associated with ALM (P=0.0226). CNV2580 is localized in the serine hydrolase-like protein (SERHL) gene and is also significantly associated with ALM (P=0.00334). Both genes are important for skeletal-muscle growth and may be relevant to OP. Although the two new CNVs are responsible for variation in ALM, more evidence is required to confirm their significance in relation to OP [79].

Therefore, the use of CNV-based GWAS in relation to OP is a cutting-edge technology and strongly supports the importance of CNV in the pathogenesis of OP. Although the results in this area are well established, it is necessary to focus on the association between classical genotypes, and actual experimentation is needed for validation. Additionally, high-throughput, sophisticated genotyping approaches for CNVs need to be optimized for further genetic screening.

6. Conclusion

OP is one of the most common diseases and is becoming more prevalent with the ageing of the world's population. BMD is the hallmark of OP and exhibits high heritability; efforts to understand OP genetic determinants have therefore been increased. OP represents a paradigm where the effects of multiple genetic factors dominate the phenotype. Although monogenic approaches that identify genes by rare mutations have contributed to the understanding of OP, the genetic background of OP is characterized by polymorphisms and variations in multiple genes; more-powerful and high-throughput technologies are needed to analyse these

aspects. Recent genetic studies in OP have facilitated the understanding of the aetiology of OP. The discovery of novel genetic factors through the use of genome sequencing will contribute to understanding the modulation of BMD and bone fragility with potential therapeutic targets. Combined with behavioural and environmental factors, findings in genetic studies can be validated and used in the development of clinical treatments of OP worldwide. There is no doubt that genetic tests have achieved significant progress in bone biology and are likely to become even more important within the next decade. To optimize accuracy, we should highlight elements including careful phenotyping, sophisticated study design, adequately powered cohorts, and multi-collaboration in future research.

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Author details

Shishu Huang[1,2], Gordon Cheung-Toa Ng[3] and Song You-Qiang[3*]

*Address all correspondence to: songy@hku.hk

1 State Key Laboratory of Oral Diseases, West China College of Stomatology, Sichuan University, PRC

2 Department of Orthopaedics and Traumatology, The University of Hong Kong, PRC

3 Department of Biochemistry, The University of Hong Kong, Pokfulam, Hong Kong SAR, PRC

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