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REVIEW

Value of rare low bone mass diseases for osteoporosis genetics

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Osteoporosis presents as increased susceptibility to fractures due to bone loss and compromised bone microstructure. Osteoporosis mainly affects the elderly population, but it is increasingly recognized that compromised bone health with low bone mass and increased fractures may have its onset already in childhood. In such cases, genetic component is likely to contribute more than lifestyle factors to disease onset. During the last decade, our understanding of the genetic determinants of osteoporosis has significantly increased through family studies, candidate gene studies and genome-wide association studies (GWASs). GWASs have led to identification of several genetic loci associated with osteoporosis. A valuable contribution to the research field has been made through studies involving families with childhood-onset rare bone diseases such as osteogenesis imperfecta, osteoporosis-pseudoglioma syndrome and various other skeletal dysplasias with reduced bone mass. Some genes involved in rare low bone mass diseases, such as *LRP5* and *WNT1,* participate in the Wnt/β-catenin pathway, and their discovery has underscored the importance of this pathway for normal skeletal health. The still continuing discovery of gene defects underlying various low bone mass phenotypes contributes to our understanding of normal bone metabolism and enables development of new therapies for osteoporosis.

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Introduction

Bone is a dynamic organ in which osteoclasts continuously break down old bone and osteoblasts form new bone. The balance between these processes is of key importance in maintaining bone mass and skeletal strength. Osteoporosis is characterized by bone mass loss and deterioration of bone microstructure resulting in increased susceptibility to fractures. Osteoporosis mainly affects the elderly population, but children and young adults may also develop osteoporotic fractures. Compared with osteoporosis occurring in post-menopausal women or older men, osteoporosis in the young population is more commonly a sign of severe primary bone pathology (primary osteoporosis) or a consequence of medications or other diseases (secondary osteoporosis). Primary osteoporosis in this age group is mainly determined by genetic factors, whereas lifestyle factors only have a minor role.[1,2]

The genetic background of osteoporosis is complex and involves several genes, many of which still remain to be identified. Mutations in genes belonging to different pathways, like the RANK-RANKL-OPG pathway (*TNFRSF11A, TNFRSF11B* and *TNFSF11*), the Wnt/β-catenin pathway (*LRP5*, *LRP6*, *WNT1* and *SOST*) and the estrogen pathway (*ESR1*), lead to deterioration of bone metabolism.[3]

During the last decades, the common approaches to determine the genetic contribution to osteoporosis have been family studies (linkage analysis), candidate gene and genome-wide association studies (GWASs). GWASs have allowed identification of >60 chromosomal loci throughout the genome that are associated with various skeletal characteristics relevant to osteoporosis, such as cortical and trabecular bone mineral density (BMD),[4–8] cortical bone thickness,[9] bone size,[10] peak bone mass and predisposition to peripheral and spinal fractures.[8,11,12] The largest GWAS meta-analysis to date was reported by Estrada *et al.*[8] In this study, 56 genome-wide loci, of which 32 were novel, were related to BMD, and 14 loci were shown to associate with fracture risk.[8] These findings have elucidated the large number of participating genes but also identified some potentially important proteins that could be targets for therapies. Despite the increasing number of interesting data, the GWAS approach has not provided much clinically useful tools to approach an individual patient with osteoporosis.

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A large number of genes related to bone mass and metabolism have been identified based on studies on rare bone diseases like osteogenesis imperfecta (OI), osteoporosis-pseudoglioma syndrome (OPPG) and various skeletal dysplasias with disturbed bone metabolism and strength. These disorders represent the extreme ends in bone mass variability, and the hypothesis is that any gene involved in such significant skeletal pathology has a major effect in the skeleton and that the same genes are likely to contribute to bone mass variability even in the normal population. This approach aims to investigate rare genetic variants in a handful of patients instead of looking for more common variants in a broader cohort of patients. The several successes over the past years have proven this approach to be valid in osteoporosis research.[13]

Recently, the growing interest toward rare skeletal phenotypes together with the increasing use of next-generation sequencing is rapidly expanding our knowledge of osteoporosis genetics.[14] Parallel to gene discoveries, these studies enhance possibilities to develop new therapies to treat the disease. This review summarizes how some genes with a major effect on low bone mass have been identified over the years through studies on rare bone diseases. We focus on monogenic forms of osteoporosis where the genes responsible for the low bone mass diseases have first been identified through family studies.

OI and Other Low Bone Mass Diseases

The most common form of bone fragility in children is OI, also known as brittle bone disease. The main hallmarks of OI include multiple fractures in association with low bone mass. Blue sclerae, dental abnormalities, skin hyperlaxity and joint hypermobility are other features that are variably present in OI.[15] The prevalence of OI is estimated to be at least one per 12 000–15 000 live births.[16]

The first systematic and widespread clinical classification of OI was presented in 1979 by Sillence *et al.*[17] It encompassed four different subgroups determined according to the clinical and radiological appearance of the patients and the inheritance pattern of the disease. Subsequently, several attempts to refine the classification have been made as new genetic forms of OI have been discovered. The several published OI classifications have used two different approaches: some take into consideration mainly the clinical and radiological phenotype, whereas others focus on the genetic and molecular causes of the disease. In this review, we use the clinical classification by Van Djik and Sillence[18] from 2014, which divides OI into five subgroups of variable severity. Type I OI includes phenotypes with mild-to-moderate severity. Patients affected by type I OI present with an increased fracture rate in addition to blue sclerae but generally no skeletal deformity or height deficit. Type II OI is lethal in the prenatal or the neonatal period, whereas type III OI, the progressively deforming form, is the most severe form in patients surviving the neonatal period. Type IV OI, denominated as 'common variable OI', is usually a relatively mild form of OI characterized by the presence of white sclerae. Finally, type V OI is a special and a homogenous form of OI presenting with calcification of the forearm interosseous membrane and formation of hyperplastic callus in fracture sites.[18]

The phenotypic variability of OI is significant but even greater is the complexity of its genetic background. Often the same gene can give rise to different types of OI severity depending on the nature and location of the mutation.[18] Mutations in one of the

Table 1 Genetic and molecular defects causing OI[18,20,21]

Gene	*Chromosomal location*	*Protein*	*Phenotype MIM number*	*Gene/locus MIM number*
Defects in collagen synthesis and structure				
COL1A1	17q21.33	Collagen alpha-1(I) chain	#166200	*120150
COL1A2	7q21.3	Collagen alpha-2(I) chain	#166210	*120160
BMP1	8p21.3	Bone morphogenetic protein 1	#614856	*112264
Defects in collagen modification-3-hydroxylation complex components				
LEPRE1	1p34.2	Prolyl 3-hydroxylase 1	#610915	*610339
CRTAP	3p22.3	Cartilage-associated protein	#610682	*605497
PPIB	15q22.31	Cyclophilin B	#259440	*123841
Defects in collagen folding and crosslink				
SERPINH1	11q13.5	Heat-shock protein 47	#613848	*600943
FKBP10	17q21.2	Peptidyl-prolyl *cis–trans* isomerase FKBP10	#610968	*607063
PLOD2	3q24	Procollagen-lysine, 2-oxoglutarate	#609220	*601865
Defects in mineralization				
IFTM5	11p15.5	Interferon-induced transmembrane protein 5	#610967	*614757
SERPINF1	17p13.3	Pigment-epithelium-derived factor	#613982	*172860
Unclassified/new genes				
SEC24D	4q26	SEC24 family member D	#616294	*607186
SPARC	5q33.1	Secreted protein, acidic, cysteine-rich	#616507	*182120
TMEM38B	9q31.2	Trimeric intracellular cation channel B	#615066	*611236
CREB3L1	11p11.2	CAMP responsive element binding protein 3-like 1	—	*616215
WNT1	12q13.12	Wingless-type MMTV integration site family, AR member 1	#615220	*164820
SP7	12q13.13	Osterix	#613849	*606633
PLS3	Xq23	Plastin 3	#300910	*300131

Abbreviations: CAMP, cyclic adenosine monophosphate; OI, osteogenesis imperfecta.

Table 2 Disorders that in addition to osteogenesis imperfecta are included in the Decreased bone density group in the 2015 Nosology and Classification of Genetic Skeletal Disorders[24]

Gene	*Syndrome*	*Chromosomal location*	*Protein*	*Phenotype MIM number*
FKBP10	Congenital brittle bones with congenital joint contractures. Bruck syndrome 1	17p21	Peptidyl-prolyl *cis–trans* isomerase FKBP10	#259450
PLOD2	Congenital brittle bones with congenital joint contractures. Bruck syndrome 2	3q24	Procollagen-lysine, 2-oxoglutarate	#609220
LRP5	Osteoporosis-pseudoglioma syndrome	11q13.2	Low-density lipoprotein receptor-related protein 5	#259770
LRP5	Primary osteoporosis	11q13.2	Low-density lipoprotein receptor-related protein 5	#166710
WNT1	Early-onset primary osteoporosis	12q13.12	Wingless-type MMTV integration site family, AR member 1	#615221
XYLT2	Spondylo-ocular dysplasia Calvarial doughnut lesions with bone fragility Idiopathic juvenile osteoporosis	17q21.33	Xylosyltransferase II	#605822 #126550 #259750
B4GALT7	Ehlers–Danlos syndrome, progeroid form Osteopenia with radiolucent lesions of the mandible	5q35	Xylosylprotein 4-betagalactosyltransferase	#130070 #166260
P4HB	Cole–Carpenter dysplasia (bone fragility with craniosynostosis)	17q25.3	Prolyl 4-hydroxylase, beta polypeptide	#112240
PYCR1	Cutis laxa, autosomal recessive form, type 2B (ARCL2B9) and 3B	17q25.3	Pyrroline-5-carboxylate reductase 1	#612940 #614438
ATP6VOA2	Cutis laxa, autosomal recessive form, type 2A (ARCL2A)	12q24.31	ATPase, Hb transporting, lysosomal, V0 subunit A2	#278250 #219200
GORAB	Geroderma osteodysplasticum	1q24.2	SCYL1-binding protein 1	#231070
IFIH1	Singleton–Merten syndrome 1	2q24.2	Interferon induced with helicase C domain 1	#182250

Abbreviation: Hb, hemoglobin.

two genes encoding type I collagen (*COL1A1* and *COL1A2*) are the most common cause and responsible for ~90% of all OI cases. These OI forms are inherited in an autosomal dominant manner.

In the last two decades, further genetic and molecular studies led to the identification of new genetic defects causing autosomal recessive forms of OI[19] (**Table 1**). Among these forms, there is a group of genetic defects interfering with the processing and folding of type I collagen in endoplasmic reticulum (ER). For example, the *CRTAP*, *PPIB* and *LEPRE1* genes encode three enzymes located in ER that are involved in the prolyl 3-hydroxylation of type I procollagen. On the other hand, two chaperones localized in the ER and encoded by the *SERPINH1*, *FKBP10* genes, and the *PLOD2* gene, are responsible for the post-transcriptional modifications of the collagen triple helix on entry into the Golgi complex. Biallelic mutations in these genes result in severe OI phenotypes.[18] Other forms of OI include defects in the mineralization process (*IFTM5* and *SERPINF1* genes). For some recently discovered OI genes such as the most recently identified *SPARC* and *SEC24D*,[20,21] the function still remains incompletely understood (**Table 1**).

In addition to the various forms of OI, there are several other genetic entities with low bone mass.[18,22–24] These syndromes may resemble OI and should be considered in differential diagnosis when assessing a patient with skeletal fragility (**Table 2**). In the following paragraphs, we describe some forms of OI or low bone mass disease more closely, to provide a more detailed description of the interesting histories leading to these genetic discoveries by family studies.

CRTAP

The *CRTAP* gene (OMIM *605497), coding for the cartilage-associated protein, is composed of seven exons and located in 3p22.3 (**Table 1**). *CRTAP* has important roles in the development of bone. Pathogenic mutations in this gene are responsible for moderate-to-severe syndromic forms of autosomal recessive OI (types II–III).[18]

The equivalent of the human *CRTAP* gene was first identified in chicken and later in mouse around two decades ago. Immunohistochemical analyses performed on those animal models revealed that the gene was expressed in most tissues during embryonal development. The same research group cloned the human *CRTAP* gene in 1999. However, the function of the encoded protein still remained unknown at that time.[25]

In 2002, Ward *et al.*[26] diagnosed four children and four adults belonging to the same family with a new form of OI. Although the phenotype of those patients closely resembled typical OI type IV, they also displayed atypical features. More importantly, the disease was inherited in an autosomal recessive manner in this consanguineous family. Subsequently, using homozygosity mapping the disease locus was mapped to chromosome 3p22-24.1, a region containing 18 genes.[26] The region did not contain any collagen genes or other genes known to associate with skeletal fragility.

Studies by Morello *et al.*[27] a few years later showed that the human *CRTAP* gene was expressed in the growth plate, in proliferating chondrocytes and in cells at the chondro-osseous junction. Most notably, it was discovered that Crtap mutant mice developed progressive and severe kyphoscoliosis and severe delay in both prenatal and postnatal growth. As the mouse phenotype matched with the phenotype in the patients described by Ward *et al.*,[26] and *CRTAP* resided within the region linked to the disease, *CRTAP* mRNA from patient skin fibroblasts was analyzed. The total amount of mRNA in the patient samples was 10% of normal, and western blot analysis showed that production of the cartilage-associated protein was decreased in the affected individuals compared with healthy controls.[27] Sequence analysis subsequently showed a homozygous loss-of-function mutation in the *CRTAP* gene in all

affected family members, confirming *CRTAP* as a novel gene associated with autosomal recessive OI.

More recently, Grafe *et al.*[28] discovered that Crtap$^{-/-}$ mice exhibit upregulated transforming growth factor-β (TGF-β) signaling; anti-TGF-β treatment corrected the bone phenotype in Crtap$^{-/-}$ mice. This finding suggests that the same treatment could be applied to some forms of OI with altered function of the TGF-β pathway.[28]

FKBP10

The *FKBP10* gene (OMIM *697063) is composed of 10 exons and located in 17q21.2. It encodes for the 65-kDa FK506-binding protein (FKBP65), a prolyl *cis–trans* isomerase. FKBP65 is the largest of the five FK506-binding proteins (FKBPs) belonging to the subfamily of immunophilins.[29] This protein acts as a molecular chaperone preventing the premature association between the procollagen chains of type I collagen in ER.[30]

FKBP10 mutations give rise to progressively deforming OI (type III)[18] (**Table 1**) and also to Bruck syndrome type I, a rare disease with congenital joint contractures and bone fragility (**Table 2**). The other form of Bruck syndrome (type II) is caused by mutations in the *PLOD2* gene and is characterized by a phenotype overlapping Bruck syndrome type I[31] (**Table 2**).

FKBP10 and its role in bone metabolism was only fairly recently discovered. In 2010, Alanay *et al.*[32] identified mutations in the *FKBP10* gene as the cause for an autosomal recessive form of OI using homozygosity mapping. In this work, the authors studied five consanguineous Turkish families diagnosed with both epidermolysis bullosa simplex (EBS) and OI. EBS was confirmed to be a separate disease caused by the absence of keratin 14 due to a null mutation in the *KRT14* gene. Taking into consideration the hypothesis that there were two co-segregating recessive disorders, the region 17q21 where *KRT14* locates became a candidate region for the OI disease gene.[32] A 0.83-Mb homozygous region containing 38 genes was subsequently identified in all affected individuals. Candidate gene mapping and mutation analysis then revealed disease-causing homozygous mutations in *FKBP10* in all affected individuals.

Since its discovery, *FKBP10* has been the focus of several studies, and the current number of detected mutations exceeds 20. Most of these pathogenic changes are biallelic frameshift mutations. The associated phenotypes range from moderate forms to severe OI with significant deformities. Furthermore, some patients presenting with congenital contractures and multiple fractures due to *FKBP10* mutations are diagnosed with Bruck syndrome type I.[31]

The Role of the Wnt/β-Catenin Pathway in Bone Phenotypes

The Wnt/β-catenin pathway is involved in a wide number of biological processes. This signaling also influences all types of bone cells (osteoblasts, osteoclasts and osteocytes) and has proven to be of remarkable importance in skeletal development, maintenance of skeletal homeostasis and in bone remodeling.[33]

Mutations in some genes functioning in the Wnt/β-catenin pathway result in low bone mass. Homozygous or compound heterozygous mutations in these genes often cause more severe disease compared with the mild phenotypes characterizing obligate carriers of the pathogenic variants. For example, biallelic mutations in the *LRP5* gene lead to OPPG and biallelic mutations in the *WNT1* gene cause OI—in both cases the phenotypes are characterized by severe and early-onset skeletal fragility due to loss-of-function in the receptor or ligand, respectively, of the WNT signaling pathway[33] (**Tables 1 and 2**). In contrast, obligate *LRP5* and *WNT1* mutation carriers display a much milder low bone mass phenotype (**Tables 1 and 2**). Some GWASs have recently shown that single-nucleotide polymorphisms (SNPs) in another member of the Wnt/β-catenin family, *WNT16*, are associated with osteoporosis and the risk of fractures.[34] Wnt10b and Wnt3a have also been implicated in low bone mass phenotypes.[35,36] However, Wnt16, Wnt10b and Wnt3a mutations have not been described in monogenic severe human osteoporosis phenotypes.

LRP5

The discovery of the *LRP5* gene (OMIM *603506) mutations in human bone pathology revealed the importance of the Wnt/β-catenin signaling in maintaining bone health in humans. *LRP5* is composed of 23 exons and located in 11q13.2; it encodes the WNT co-receptor low-density lipoprotein receptor-related protein 5. LRP5 together with frizzled activates the Wnt/β-catenin pathway by binding Wingless (Wnt).[37] As mentioned earlier, loss-of-function mutations in *LRP5* cause OPPG, an autosomal recessive disease with severe childhood-onset osteoporosis and congenital or juvenile blindness (**Table 2**). Other clinical features characterizing this condition include deformities due to recurrent fractures, and glioma-like eye phenotype; atypical femoral fractures have also been described.[38]

In 1996, the OPPG locus was mapped to 11q12-13 based on studies on a cohort of patients and families affected by OPPG. This information was achieved using the traditional linkage analysis combined with the homozygosity mapping. At that time, patients with OPPG syndrome were known to not have defects in collagen synthesis, systemic hormones, calcium homeostasis, endochondral growth or bone turnover. However, the pathogenic mechanism of the disease as well as a robust candidate gene still remained unknown.[39]

Five years later, the positional candidate approach allowed Gong *et al.*[40] to identify the *LRP5* gene and loss-of-function mutations as the causative for OPPG syndrome. Notably, it was also discovered that both children and adults with heterozygous *LRP5* mutations display an increased incidence of osteoporosis and fractures.[41]

During the following years, many candidate gene-association studies showed a correlation between some SNPs in the *LRP5* gene and BMD in the general population.[4] These results have been confirmed in GWAS.[37] In 2008, Richards *et al.*[42] found an association between the rs3736228 SNP in *LRP5* and lumbar spine and femoral neck BMDs; individuals with this SNP are inclined to osteoporosis and increased risk of fracture. In another study, Val667Met and Ala1330Val *LRP5* polymorphisms were also shown to be involved in BMD.[43]

WNT1

WNT1 (OMIM *164820) is one more gene belonging to the Wnt/β-catenin pathway and having a role in the maintenance of bone mass.[44] The *WNT1* gene encodes the wingless-type MMTV integration site family, member 1. It is clustered with another member of the same family, *WNT10B*, in the chromosomal region 12q13.[45] The Wnt1 protein regulates the

canonical Wnt pathway by binding to the dual frizzled-LRP5 receptor. Since 2001, it was known that Wnt1 influences craniofacial phenotypes in Wnt1-Cre transgenic mice and has a role in brain development.[46]

In 2013, three research groups identified homozygous mutations of *WNT1* in patients affected by OI using exome-sequencing and homozygosity mapping and showed that WNT1 has a significant role in bone metabolism.[44,47,48] The identified mutations in *WNT1* gave rise to OI with moderate-to-severe phenotype. Notably, a heterozygous missense mutation in *WNT1* was found to segregate in an autosomal dominant manner in a family in which several members were affected by early-onset osteoporosis and fractures.[48] Affected subjects were of normal adult height and lacked major skeletal deformities and extra-skeletal manifestations but developed significant kyphosis due to vertebral compression fractures at an early age; bone biopsies confirmed abnormal bone microarchitecture and low bone turnover.[48] These findings prove that osteoporosis related to *WNT1* gene mutations can follow both autosomal recessive and autosomal dominant pattern of inheritance, respectively causing OI (types III–IV; **Table 1**) and early-onset osteoporosis.[47,48]

Mice with mutated *Wnt1* have malformation of the anterior cerebellum.[37] Patients with *WNT1* mutations may also present with developmental defects in the central nervous system.[14] Recently, a thorough evaluation of skeletal phenotype in *Wnt1*-knockout mice showed that the mice were in fact prone to fractures and displayed osteopenia, in addition to the brain defects, thus confirming the role of *Wnt1* in determining the bone phenotype.[49]

Contribution of Rare Skeletal Phenotypes to New Therapies

The discovery of new genes involved not only in low bone mass but also in high bone mass phenotypes has made a remarkable contribution toward establishing new therapies for osteoporosis. Maintenance of bone health requires balance between two opposing mechanisms: bone formation and resorption. Bone resorption requires osteoclastic proteins that degrade extracellular matrix.

As described earlier, loss-of-function mutations in *LRP5* cause OPPG. However, gain-of-function mutations give rise to high bone mass phenotypes, as first shown in a large family with increased BMD.[50] The LRP5 function is normally inhibited by sclerostin (SOST) and Dickkopf homolog-1. The gain-of-function mutations in *LRP5* render the receptor resistant to these inhibitors, thus allowing Wnt/β-catenin signaling and consequent bone formation above the normal levels. Similarly in Van Buchem's disease and sclerosteosis loss-of-function mutations in *SOST* result in uninhibited Wnt/β-catenin signaling.[51] These results have been confirmed in several human studies and in transgenic murine models.[52] Observations from both low and high bone mass diseases have elucidated the great therapeutic potential that lies in the modulation of Wnt/β-catenin signaling and led to the idea that a SOST antibody could be used to increase bone mass in patients with osteoporosis; first results from treatment trials are promising.[53] Along the same lines, studies on patients with osteopetrosis have led to the development of drugs that target specifically osteoclastic bone resorption machinery and aim to maintain bone mass by reducing bone resorption while allowing osteoblastic bone formation.[54] Cathepsin K is an osteoclastic enzyme responsible for degradation of type I collagen. Loss-of-function mutations in the cathepsin K gene (*CTSK*) cause pycnodysostosis, a rare autosomal recessive disease associated with increased bone mass.[55] Increased understanding of the pathogenetic mechanisms in pychnodysostosis has led to the development of odanacatib, a cathepsin K inhibitor, which in clinical trials has shown promising results in the treatment of osteoporosis.[56,57]

Conclusions

Several different methods have been applied to explore the genetic causes of osteoporosis in order to better define its still inadequately understood pathogenesis. Several major genes relevant to normal bone homeostasis and the development of osteoporosis have been discovered by studying single families and small cohorts of patients with rare bone diseases. These severe phenotypes with low bone mass represent the extreme end of the spectrum in bone mass variability and are therefore optimal targets for discovery of genes with a major role in bone metabolism. The recent developments in genetic methodology and the increased availability and affordability of next-generation sequencing techniques are likely to further promote gene discoveries. These increase our understanding of the complex networks regulating bone health but may, optimally, also open new avenues for drug development.

Interestingly, the genes that in GWAS associate with BMD and fractures in large population-based cohorts seem not to significantly overlap with the genes that have been identified in monogenic forms of OI or osteoporosis. Only one gene underlying OI, *SP7*, and two genes responsible for monogenic diseases with decreased bone density, *LRP5* and *RUNX2,* showed an association with skeletal outcomes in the largest genome-wide meta-analyses.[8] *LRP5* gene, first identified in studies involving families with OPPG,[40] has been significantly associated with skeletal features in several GWASs.[8,58] *RUNX2* mutations cause cleidocranial dysplasia, but the gene also associates with low BMD in the general population.[8] GWASs provide a powerful tool to discover pathways that are important for osteoporosis in the general population and may have therapeutic potential, and therefore GWASs in large population-based cohorts and small-scale family studies complement each other.

The time lag from gene discoveries to introduction of new clinically available therapies is still very long, but hopefully scientific and methodological advancements will enhance even these processes in the future. Further, as seen in the presented examples, the genetic background and the resulting bone pathology in osteoporosis are diverse, and therefore more personalized treatment plans, based on the specific genetic cause and consequent molecular mechanism underlying each case of osteoporosis, are required in the future as the therapeutic arsenal expands.

Materials and Methods

Articles for this Review were identified by searching the PubMed database, using terms including 'osteogenesis imperfecta', 'osteoporosis', 'fracture', 'GWAS', 'CRTAP', 'FKBP10', 'Wnt/β-catenin', 'WNT1', 'LRP5', 'bisphosphonates',

'SOST' and 'cathepsin K', alone and in combination. Only full-text English-language papers were included. Papers were selected for inclusion according to the authors' opinion of their relevance to the subject, with preference given to publications within the past 20 years. Searches were performed through April–May 2015.

Conflict of Interest

The authors declare no conflict of interest.

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