Bone & Skeletal Aging Genetic Pathway Reference

A standalone educational reference: pathway biology, gene catalogue, SNP lookup, and supplement targets

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Disclaimer

This document is an educational reference about bone and skeletal genetics. It does not constitute medical advice, does not establish a clinician-patient relationship, and is not a substitute for individualized clinical evaluation. Common-variant bone genetics modulates risk in the range of 0.02–0.20 SD per allele for bone mineral density and odds-ratio increments of roughly 1.1–1.3 for fracture risk; cumulative significance arises from convergent patterns and from interaction with calcium intake, vitamin D status, mechanical loading, sex steroids, and concomitant medications. Any individual interpretation must be made by a qualified clinician with access to the full clinical context, including DXA, fracture history, secondary causes, and current medications.

1. Pathway biology

1.1 Why bone genetics matters

Bone is metabolically active connective tissue maintained by lifelong remodeling. Across adulthood about 5–10 percent of the skeleton is replaced every year through coupled cycles of osteoclastic resorption and osteoblastic formation. Peak bone mass is reached around age 25–30, plateaus through the 30s, and declines thereafter — slowly in men (about 0.5–1 percent per year) and abruptly in women at menopause (3–5 percent per year for about 5 years, then back to about 1 percent per year). Heritability of bone mineral density is high: twin and family studies put it at 60–80 percent (Ralston and Uitterlinden, Endocrine Reviews 2010). Genetics dominates peak bone mass; environment dominates the rate of loss.

Three GWAS waves anchor the modern field. Estrada et al., Nature Genetics 2012 (the GEFOS-2 meta-analysis, n=32,961) identified 56 BMD loci, of which 14 also predicted fracture and 6 reached genome-wide significance for fracture. Kemp et al., Nature Genetics 2017 (UK Biobank heel ultrasound BMD, n=142,487) identified 203 loci. Morris et al., Nature Genetics 2019 (UK Biobank, n=426,824) identified 518 loci explaining about 20 percent of the phenotypic variance. These analyses converge on five mechanistically coherent gene families: the Wnt/β-catenin pathway, the RANK/RANKL/OPG axis, the vitamin D system, sex-steroid signaling, and the bone matrix proteins.

1.2 The cellular triad

Bone remodeling is performed by three cell types operating in coupled units called bone multicellular units (BMUs). Osteoblasts derive from mesenchymal stem cells (MSCs); their commitment is driven by the master transcription factors RUNX2 and SP7 (Osterix), and they secrete the osteoid scaffold composed predominantly of type I collagen (COL1A1 and COL1A2 chains, about 95 percent of bone matrix protein), plus the non-collagenous proteins osteocalcin (BGLAP), osteopontin (SPP1), bone sialoprotein, and matrix extracellular phosphoglycoprotein

(MEPE). The osteoid then mineralizes into hydroxyapatite, gated by tissue-nonspecific alkaline phosphatase (ALPL) which hydrolyzes pyrophosphate, the principal endogenous mineralization inhibitor.

Osteoclasts derive from the monocyte-macrophage lineage; their differentiation is driven by RANKL (TNFSF11) binding to RANK (TNFRSF11A) on the osteoclast precursor. Mature osteoclasts seal a resorption lacuna against bone, acidify it via vacuolar H^+-ATPase, and secrete cathepsin K (CTSK) to digest the demineralized matrix. The resulting collagen fragments, including the C-terminal telopeptide (CTX) and N-terminal telopeptide (NTX), are released into circulation and serve as biomarkers of bone resorption.

Osteocytes are terminally differentiated osteoblasts entombed in the mineralized matrix within lacunae and interconnected through canaliculi by long dendritic processes. They constitute about 95 percent of bone cells and serve as the central regulator of remodeling. Osteocytes mechanosense — they detect interstitial fluid shear stress generated by skeletal loading — and translate that signal into changes in sclerostin (SOST) secretion: under load, SOST is suppressed and Wnt signaling is permitted in osteoblast precursors, driving formation; under unloading or microdamage, SOST is induced and formation is suppressed. Osteocytes also produce RANKL, FGF23, and DKK1, making them simultaneously the brake on formation and the driver of resorption.

1.3 The Wnt/β-catenin axis: the master osteoanabolic switch

Canonical Wnt signaling is the dominant osteoanabolic cascade. Wnt ligands (especially WNT16, WNT3, WNT4, WNT5B, WNT10B in bone) bind LRP5 or LRP6 co-receptors and Frizzled (FZD) receptors at the osteoblast precursor surface. Receptor engagement inhibits the destruction complex (composed of GSK3β, CK1α, AXIN1, and APC) that would otherwise phosphorylate β-catenin and target it for proteasomal degradation. Stabilized β-catenin translocates to the nucleus and partners with TCF/LEF transcription factors to drive osteoblastogenesis, suppress osteoblast apoptosis, and induce osteoprotegerin (OPG) expression — thereby suppressing osteoclastogenesis indirectly. WNT16 specifically acts on this OPG-inducing axis and is the strongest single GWAS signal for BMD in the WNT family (Medina-Gomez et al., PLoS Genetics 2012; Estrada et al., Nature Genetics 2012; Zheng et al., PLoS Genetics 2012).

Three classes of endogenous Wnt antagonists fine-tune this signal. Sclerostin (SOST) is secreted predominantly by osteocytes and binds the LRP5/6 extracellular domain, blocking ligand-receptor engagement. Dickkopf-1 (DKK1) binds LRP5/6 in cooperation with Kremen receptors. Secreted Frizzled-related proteins (sFRPs) compete with FZD receptors for Wnt ligands. Loss-of-function mutations in SOST cause sclerosteosis (severe bone overgrowth, OMIM 269500); deletion of a 52-kb downstream regulatory enhancer (the Van Buchem deletion) causes Van Buchem disease (OMIM 239100); both produce extreme high-bone-mass phenotypes. These observations were the molecular rationale for romosozumab, the anti-sclerostin monoclonal antibody approved in 2019. Loss-of-function mutations in LRP5 cause osteoporosis-pseudoglioma syndrome (OMIM 259770); gain-of-function mutations in the LRP5 first β-propeller domain (the SOST/DKK1 binding region) cause autosomal-dominant high-bone-mass syndrome (Boyden et al., NEJM 2002; Gong et al., Cell 2001).

1.4 The RANKL/RANK/OPG axis: the master osteoclast switch

Receptor activator of NF-κB ligand (RANKL, encoded by TNFSF11), produced by osteoblasts, osteocytes, and activated T cells, binds RANK (TNFRSF11A) on the osteoclast precursor surface and drives differentiation, fusion, and activation. Osteoprotegerin (OPG, encoded by

TNFRSF11B) is a soluble decoy receptor secreted by osteoblasts and osteocytes that binds and sequesters RANKL, blocking RANK engagement. The RANKL:OPG ratio, not the absolute level of either, sets the resorption rate.

Estrogen, vitamin D, mechanical loading, and PTH all modulate this ratio. Estrogen is the most potent endogenous suppressor of RANKL and inducer of OPG, which is why estrogen withdrawal at menopause produces the abrupt 3–5 percent per year BMD loss. Glucocorticoids do the opposite — they suppress OPG and induce RANKL, which is why supraphysiologic glucocorticoid exposure produces rapid bone loss. Continuous PTH elevation suppresses OPG and drives resorption (the mechanism of primary hyperparathyroidism); pulsatile PTH (the mechanism of teriparatide) instead drives osteoblastogenesis. Denosumab, the monoclonal antibody against RANKL, is the pharmacological exploitation of this axis. Loss-of-function mutations in TNFRSF11A (RANK) cause autosomal recessive osteopetrosis; loss-of-function in TNFRSF11B (OPG) causes juvenile Paget disease (OMIM 239000).

1.5 The vitamin D system: substrate, transport, activation, catabolism, receptor

Vitamin D regulates intestinal calcium absorption, renal calcium reabsorption, and direct osteoblast/osteoclast differentiation. The pathway has five sequential stages, each with genetic variation.

Cutaneous synthesis. UVB photolysis of 7-dehydrocholesterol in epidermal keratinocytes produces previtamin D3, which thermally isomerizes to vitamin D3 (cholecalciferol). Skin pigmentation, latitude, age, and sunscreen use all modulate this step; there is no major common SNP in this stage.

Transport. Vitamin D3 is hydrophobic and circulates bound to the vitamin D binding protein (DBP, encoded by GC), with a small fraction on albumin and a tiny free fraction. The GC gene is highly polymorphic; rs2282679, rs7041, and rs4588 define the three major DBP isoforms (Gc1f, Gc1s, Gc2) that differ in vitamin D affinity and clearance. rs2282679 is the strongest serum 25(OH)D GWAS signal (Wang et al., Lancet 2010; Jiang et al., Nature Communications 2018, n=417,580).

25-hydroxylation. The liver enzyme CYP2R1 (and to a lesser extent CYP27A1) hydroxylates vitamin D3 at carbon 25 to produce 25-hydroxyvitamin D (calcidiol), the storage form measured clinically. CYP2R1 is rate-limiting; rs10741657 and rs12794714 in the CYP2R1 promoter are the second-strongest 25(OH)D GWAS locus after GC.

1α-hydroxylation. The renal proximal tubule enzyme CYP27B1 converts 25(OH)D to the hormonally active 1,25-dihydroxyvitamin D (calcitriol). This step is tightly regulated by PTH (induces), FGF23 (suppresses), and $1,25(OH)_2D$ itself (suppresses, via short feedback).

Catabolism. CYP24A1 hydroxylates 25(OH)D and $1,25(OH)_2D$ at carbon 24, initiating their inactivation cascade to calcitroic acid. CYP24A1 is induced by $1,25(OH)_2D$ in a feed-forward loop. Loss-of-function CYP24A1 mutations cause idiopathic infantile hypercalcemia (OMIM 143880); the common variant rs6013897 modestly modulates 25(OH)D levels.

Receptor. The vitamin D receptor (VDR) is a nuclear hormone receptor that heterodimerizes with the retinoid X receptor (RXR) and binds vitamin D response elements (VDREs) in target gene promoters. VDR target genes include CYP24A1 (negative feedback), TRPV6 (intestinal calcium channel), CALB (calbindin), and BGLAP (osteocalcin). Five common VDR polymorphisms have been studied for decades: FokI (rs2228570) at the start codon, BsmI

(rs1544410) and ApaI (rs7975232) in intron 8, TaqI (rs731236) in exon 9, and Cdx2 (rs11568820) in the intestine-specific promoter.

Cofactors and substrates. CYP2R1, CYP27B1, and CYP24A1 are heme-thiolate cytochrome P450 enzymes that require heme iron, NADPH, and adrenodoxin/adrenodoxin reductase for electron transfer. RXR requires 9-cis retinoic acid for full activity. VDR transcriptional activity at VDREs depends on coactivators (NCOA family) and on the chromatin context.

1.6 Sex steroids: estrogen, androgen, aromatase

Sex steroids restrain bone resorption in both sexes. In women, estradiol is the dominant signal; estrogen withdrawal at menopause produces the well-characterized rapid bone loss. In men, the relationship is more complex: serum estradiol — much of which is produced by aromatization of testosterone via CYP19A1 in adipose, bone, and brain — is a stronger predictor of male BMD than testosterone itself, particularly after age 60 (Khosla et al., JCEM 2008). Men with aromatase deficiency or estrogen receptor α (ESR1) loss-of-function develop osteoporosis despite normal or elevated testosterone (Smith et al., NEJM 1994; Morishima et al., JCEM 1995).

ESR1 (estrogen receptor α) is the dominant receptor in bone; ESR2 (estrogen receptor β) plays a smaller and partly opposing role. The classical ESR1 polymorphisms PvuII (rs2234693, intron 1) and XbaI (rs9340799, intron 1) form a haplotype that has been studied across more than 30 cohorts (Genomos consortium, Ioannidis et al., JAMA 2004, n=18,917). The XbaI G allele (X) and PvuII C allele (P) on the same haplotype (PX) appear modestly protective for fracture, although main effects on BMD are inconsistent.

Sex hormone binding globulin (SHBG) sets the free fraction of testosterone and estradiol. SHBG common variants (notably rs1799941) modulate SHBG levels and therefore bioavailable sex steroid; this is most relevant in men, where free testosterone is the more bone-relevant fraction.

Androgen receptor (AR) signaling contributes directly via the AR CAG repeat (longer repeat = less active AR) and indirectly via aromatization. CYP19A1 polymorphisms — rs10046 in the 3′ UTR is the most studied — modulate aromatase activity and serum estradiol in men.

1.7 Calcium-phosphate-FGF23 mineral homeostasis

Bone mineralization requires calcium and phosphate at the osteoid front. Calcium is gated at three nodes: intestinal absorption (vitamin-D-dependent active transport via TRPV6/CALB and passive paracellular transport; rate-limited by $1,25(OH)_2D$), renal reabsorption (TRPV5 in the distal tubule, regulated by Klotho), and the calcium-sensing receptor (CASR) on parathyroid cells, which suppresses PTH secretion when serum ionized calcium is high. The CASR A986S polymorphism (rs1801725) shifts the Ca^{2+} set-point modestly.

Phosphate is regulated by FGF23, secreted by osteocytes in response to elevated phosphate or $1,25(OH)_2D$. FGF23 acts on the kidney via FGFR1 and the obligate co-receptor αKlotho (encoded by KL) to suppress NaPi2a/2c phosphate reabsorption and to suppress CYP27B1, lowering $1,25(OH)_2D$. Klotho also has FGF23-independent effects on calcium handling and on systemic aging; the KLOTHO KL-VS haplotype (rs9536314, F352V) is associated with longevity, higher HDL, and lower stroke risk.

1.8 Bone matrix and mineralization gates

Type I collagen is a heterotrimer of two α1 chains (COL1A1) and one α2 chain (COL1A2). The COL1A1 Sp1 polymorphism (rs1800012, intron 1, G>T) lies in a transcription factor binding site; the T (S) allele increases COL1A1 transcription, which paradoxically WEAKENS bone because it shifts the α1:α2 ratio away from the optimal 2:1 (Mann et al., Journal of Clinical Investigation 2001). Severe COL1A1 or COL1A2 loss-of-function mutations cause osteogenesis imperfecta (OMIM 166200, 166210, 166220, 259420).

Osteocalcin (BGLAP) is the most abundant non-collagenous protein in bone. Its bone-binding function depends on γ-carboxylation of three glutamate residues by GGCX, which uses reduced vitamin K (vitamin K hydroquinone) as a cofactor. VKORC1 regenerates the reduced vitamin K. The VKORC1 promoter variant rs9923231 (well known from warfarin pharmacogenetics; CPIC level A) also modulates the vitamin K cycle and therefore the carboxylation status of osteocalcin and Matrix Gla Protein.

Mineralization is gated by ALPL (tissue-nonspecific alkaline phosphatase). ALPL hydrolyzes pyrophosphate, an endogenous mineralization inhibitor. Severe ALPL loss-of-function causes hypophosphatasia (OMIM 241500, 241510, 146300) — a clinical spectrum from neonatal lethality to adult-onset stress fractures and dental disease. Common ALPL variants modulate serum ALP within the normal range.

1.9 Mechanical loading

Skeletal loading produces interstitial fluid shear stress in the canalicular network surrounding osteocytes. The osteocyte translates this mechanical signal into transcriptional output principally by suppressing SOST: loaded bone secretes less sclerostin, Wnt signaling is permitted, and osteoblast formation increases at the loaded site (Robling et al., Journal of Biological Chemistry 2008). Disuse — bedrest, microgravity, denervation, immobilization — produces the inverse: SOST rises, Wnt is suppressed, and rapid bone loss ensues. The mechanostat operates within minutes for SOST mRNA changes and over weeks for measurable BMD changes.

Loading magnitude, rate, and direction all matter. Resistance training, plyometric loading, and impact (running, jumping) drive larger osteogenic responses than equivalent-energy steady-state aerobic exercise (Beck et al., Journal of Bone and Mineral Research 2017). The genetic background — particularly LRP5, WNT16, and SOST genotype — modifies the magnitude of the loading response.

2. Gene catalogue by functional category

Each subsection below presents the genes in one functional category, with rsIDs, common variant names, functional consequences, GWAS-derived effect sizes where available, ClinVar pathogenicity status ("benign" / "likely benign" / "VUS" / "likely pathogenic" / "pathogenic" / "risk factor" / "none" for unannotated common variants), and PharmGKB clinical annotation level (1A highest evidence, 4 lowest, or "none" if not annotated). Cofactor requirements are flagged where they bear on supplementation.

2.1 Wnt/β-catenin pathway — master osteoanabolic switch

LRP5 / LRP6 — Wnt co-receptors

Gene	rsID	Variant	Functional / clinical interpretation

LRP5	rs3736228	A1330V (exon 18 missense)	T (V allele) reduces LRP5 Wnt-signal output. Meta-analysis (Liu, BioMed Res Int 2014, 7 case-control studies) — V carriers about 19 percent higher osteoporosis/fracture risk (OR 1.19). Effect strongest in men. ClinVar: risk factor. PharmGKB: 4.
LRP5	rs4988321	V667M (exon 9 missense)	A (M allele) reduces Wnt signaling. Cross-sectional n=889; haplotype with rs3736228 explains up to 15 percent of male peak BMC variance (Saarinen, Calcif Tissue Int 2009). ClinVar: risk factor. PharmGKB: none.
LRP5	rs41494349	Q89R (exon 2 missense)	G (R allele) — Asian-specific risk allele for low BMD (Urano, J Bone Miner Metab 2009). Rare in Europeans. ClinVar: VUS/risk factor.
LRP5	rs2306862	N740N (synonymous)	T allele — Asian BMD modulator, in LD with rs3736228 (Koay, J Bone Miner Res 2004). ClinVar: benign.
LRP5	rs4988300	intronic	GG genotype — lower BMD and lower P1NP in elderly Chinese (Zhu, Front Endocrinol 2020). ClinVar: none.
LRP5	rs634008	intronic	TT genotype — lower BMD/PINP in elderly with osteoporosis (Zhu, Front Endocrinol 2020). ClinVar: none.
LRP5 (rare)	various	Severe LoF (R494Q etc.)	Pathogenic; cause osteoporosis-pseudoglioma syndrome (OMIM 259770). Rare LoF in HBM-causing first β-propeller domain (G171V/R, T253I, etc.) cause autosomal-dominant high-bone-mass (Boyden NEJM 2002). ClinVar: pathogenic.
LRP6	rs10743980 region	intronic	Modest BMD signal, less-replicated. ClinVar: none.

LRP5 missense variants in the third β-propeller domain (rs3736228 A1330V and rs4988321 V667M) are loss-of-function for Wnt signal transduction; the rare HBM-causing variants in the first β-propeller domain (where SOST/DKK1 bind) are gain-of-function. These two domains thus map to opposite phenotypes and the gene as a whole is bidirectional with respect to BMD.

WNT16 / CPED1 region — strongest BMD GWAS Wnt locus

Gene	rsID	Variant	Functional / clinical interpretation
WNT16	rs3801387	intronic; in perfect LD with rs917727	Lead BMD GWAS SNP at the 7q31.31 locus. Meta-analysis $P=2.6\times10^{-31}$, n≈14,000; effect explains 0.6–1.8 percent of total-body BMD variance (Medina-Gomez, PLoS Genet 2012). Replicated in Estrada GEFOS-2 2012. Allele lowering

			BMD: minor allele. ClinVar: risk factor.
WNT16	rs917727	intronic; perfect LD partner of rs3801387	Discovery SNP in Medina-Gomez 2012, $P=4.1\times10^{-11}$ in children; lead SNP in pediatric and adult populations. ClinVar: risk factor.
WNT16	rs2707466	Thr→Ile missense	C allele −0.11 SD cortical bone thickness, $P=6.2\times10^{-9}$ (Zheng, PLoS Genet 2012). Forearm fracture OR 1.22, $P=7.2\times10^{-6}$. ClinVar: risk factor.
WNT16	rs2908004	Gly→Arg missense	G allele −0.16 SD forearm BMD, $P=1.2\times10^{-15}$ (Zheng 2012). ClinVar: risk factor.
WNT16	rs55710688	Kozak sequence (5′ UTR ins)	Minor allele eQTL for FAM3C; Bonferroni-significant BMD association (Pérez-Núñez, Sci Rep 2018). ClinVar: none.
WNT16	rs142005327	putative enhancer	eQTL; Bonferroni-significant BMD association (Pérez-Núñez 2018). ClinVar: none.
WNT16 (rare)	rs190011371	3′ UTR	Rare variant overrepresented in low-BMD women in the BARCOS cohort (Pérez-Núñez 2018). ClinVar: VUS.

WNT16 is the single strongest BMD GWAS Wnt-family signal. WNT16 specifically increases osteoblast OPG expression and thereby suppresses osteoclastogenesis indirectly. The CPED1-WNT16 locus contains two independent BMD signals — one near WNT16 (rs3801387) and one near CPED1 (rs13245690) — that act on different regulatory elements (Tang et al., bioRxiv 2021).

SOST and the Van Buchem regulatory region — Wnt brake

Gene	rsID	Variant	Functional / clinical interpretation
SOST	rs1234612	promoter/ regulatory	G allele higher sclerostin, lower BMD (Estrada 2012; Velázquez-Cruz, PLoS One 2014). ClinVar: risk factor.
SOST	rs1513670	downstream regulatory	A allele higher SOST, lower BMD. GWAS-replicated (Sims, J Bone Miner Res 2008; Estrada 2012; Yerges 2010). ClinVar: risk factor.
SOST	rs7220711	within Van Buchem 52-kb deletion region	A allele higher SOST expression via altered MAFB binding (Maupin et al., Bone 2019, ChIP and reporter assays). ClinVar: risk factor.
SOST	rs1107748	within Van Buchem deletion region	C allele higher SOST expression via altered CTCF binding (Maupin 2019). ClinVar: risk factor.
SOST	rs9902563	downstream regulatory	Tag SNP in LD block with rs1513670 (Yerges 2010). ClinVar: none.

SOST	rs851056 / rs851054	downstream / 3′ flanking	Modulate SOST levels in elderly cohorts (Sims 2008). ClinVar: none.
SOST	rs1230399	promoter	Promoter variant; modest BMD signal. ClinVar: none.
SOST	rs74252774	5′ regulatory	Less-replicated. ClinVar: none.
SOST (rare)	various LoF	splice/truncating	Pathogenic; cause sclerosteosis (autosomal recessive, OMIM 269500). ClinVar: pathogenic.
SOST 52-kb downstream deletion	structural	long-range enhancer (ECR5)	Pathogenic; cause Van Buchem disease (OMIM 239100). Not detectable by standard SNP calling — requires structural-variant analysis. ClinVar: pathogenic.
DKK1	rs1569198	intronic	10q21 locus; A allele higher DKK1, lower BMD; fracture-associated in Estrada 2012 (genome-wide significant for fracture).
DKK1	rs1896367	intronic	Tag SNP in same LD block as rs1569198. ClinVar: risk factor.

Sclerostin is the single most therapeutically actionable Wnt-pathway target. Romosozumab (Evenity), a monoclonal antibody against sclerostin, was approved in 2019 for postmenopausal osteoporosis at high fracture risk; in the FRAME trial (Cosman, NEJM 2016) it reduced new vertebral fractures by 73 percent at 12 months versus placebo. The Van Buchem deletion (52 kb downstream of SOST) shows that long-range regulatory variation is the dominant common-variant driver at this locus; standard SNP-based analyses will miss this structural variant.

Wnt downstream and other antagonists

Gene	rsID	Variant	Functional / clinical interpretation
CTNNB1 (β-catenin)	rs430727 region	intronic	Modest BMD effect (Estrada 2012). Severe LoF causes exudative vitreoretinopathy and other syndromes. ClinVar: variable.
AXIN1	rs9921222	intronic	Minor allele reduced BMD (Estrada 2012). AXIN1 part of the destruction complex. ClinVar: risk factor.
SFRP4	rs1721400 region	intronic	GWAS-suggestive BMD effect. ClinVar: none.
WNT4	rs6532023 region	intronic	BMD-associated (Estrada 2012). ClinVar: risk factor.
WNT3	rs7224998 region	intronic	BMD-associated (Estrada 2012). ClinVar: none.
WNT5B	rs2887571 region	intronic	BMD-associated (Estrada 2012). ClinVar: none.
WNT10B	rs1051886 region	exonic	Rare LoF causes Tetraamelia syndrome (OMIM 273395).

2.2 RANK / RANKL / OPG — master osteoclast switch

Gene	rsID	Variant	Functional / clinical interpretation
TNFSF11 (RANKL)	rs9594738	intergenic	T allele about 0.6 percent lumbar spine BMD decrease per allele (Estrada 2012, $P<10^{-10}$). ClinVar: risk factor.
TNFSF11 (RANKL)	rs9594759	intergenic	C allele lower BMD; replicated in Styrkarsdottir, NEJM 2008. ClinVar: risk factor.
TNFRSF11A (RANK)	rs884205	intronic	T allele higher fracture risk; Estrada 2012 fracture-associated locus.
TNFRSF11A (RANK)	rs9646629 region	intergenic	BMD-associated, smaller effect. ClinVar: none.
TNFRSF11B (OPG)	rs6469804	intronic	C allele lower OPG, lower BMD (Styrkarsdottir 2008; Estrada 2012). ClinVar: risk factor.
TNFRSF11B (OPG)	rs2073618	1181 G>C, K3N (signal peptide)	G allele reduced OPG signal peptide cleavage, lower OPG, lower BMD (Hsu, JBMR 2006); meta-analysis (Guo, Hum Genet 2010). ClinVar: risk factor.
TNFRSF11B (OPG)	rs4355801	intergenic	A allele lower BMD, higher fracture (Styrkarsdottir 2008). ClinVar: risk factor.
TNFRSF11B (OPG)	rs6993813 / rs7812088 / rs6469792	intronic / intergenic	Tag SNPs in same LD block; modulate OPG levels in elderly cohorts. ClinVar: none/risk factor.
TNFRSF11A (rare)	various LoF	truncating	Pathogenic; autosomal recessive osteopetrosis (OMIM 612301). Loss of activating function. ClinVar: pathogenic.
TNFRSF11B (rare)	various LoF	truncating	Pathogenic; juvenile Paget disease (idiopathic hyperphosphatasia, OMIM 239000). ClinVar: pathogenic.

Denosumab is the pharmacological antagonist of RANKL and is the most potent currently-approved antiresorptive for postmenopausal osteoporosis (FREEDOM trial, Cummings NEJM 2009: 68 percent reduction in vertebral fracture, 40 percent in hip fracture at 36 months). Denosumab effect is reversible on discontinuation, with rebound resorption that has produced multiple vertebral fractures in some patients within 6–18 months of stopping — the standard recommendation is to transition to a bisphosphonate at the time of denosumab discontinuation (Tsourdi, JCEM 2017).

2.3 Vitamin D system — substrate, transport, activation, catabolism, receptor

2.3a Transport (vitamin D binding protein)

Gene	rsID	Variant	Functional / clinical interpretation

GC	rs2282679	intron 12 T>G	Strongest 25(OH)D GWAS signal. G allele 5–10 percent lower 25(OH)D per allele. SUNLIGHT consortium n=33,996 $P<10^{-50}$ (Wang Lancet 2010); n=417,580 (Jiang Nat Commun 2018). ClinVar: risk factor.
GC	rs7041	exon 11 T>G (D432E)	G→Gc1f (faster clearance). Defines DBP isoform with rs4588. ClinVar: risk factor.
GC	rs4588	exon 11 C>A (T436K)	A→Gc2 isoform; lower DBP affinity for 25(OH)D. Linked with rs7041; defines Gc1f/Gc1s/Gc2 haplotypes. ClinVar: risk factor.

2.3b 25-hydroxylation (liver)

Gene	rsID	Variant	Functional / clinical interpretation
CYP2R1	rs10741657	promoter A>G	G allele about 0.06 SD/allele lower 25(OH)D. $P<10^{-40}$ (Ahn HMG 2010; Jiang 2018). ClinVar: risk factor.
CYP2R1	rs12794714	promoter	T allele lower 25(OH)D (Jiang 2018). ClinVar: risk factor.

Cofactors: CYP2R1 is a heme-thiolate cytochrome P450 — requires heme iron and NADPH.

2.3c 1α-hydroxylation (kidney)

Gene	rsID	Variant	Functional / clinical interpretation
CYP27B1	rs10877012	promoter G>T	T reduced $1,25(OH)_2D$ synthesis (Bailey, Diabetes 2007). ClinVar: risk factor.
CYP27B1 (rare)	various LoF	truncating	Pathogenic; vitamin D-dependent rickets type 1A (OMIM 264700). ClinVar: pathogenic.

2.3d Catabolism

Gene	rsID	Variant	Functional / clinical interpretation
CYP24A1	rs6013897	intronic A>T	T higher CYP24A1, faster 25(OH)D catabolism, lower 25(OH)D (Wang 2010 SUNLIGHT). ClinVar: risk factor.
CYP24A1	rs17216707	intronic	T modulates catabolism (Manousaki, AJHG 2017). ClinVar: risk factor.
CYP24A1 (rare)	various LoF	truncating	Pathogenic; idiopathic infantile hypercalcemia (OMIM 143880). ClinVar: pathogenic.

2.3e Vitamin D receptor (VDR)

Gene	rsID	Variant	Functional / clinical interpretation

VDR	rs2228570 (FokI)	exon 2 start codon T>C	Two start codons; the F (short, more active) isoform is associated with stronger downstream VDR signaling. Nomenclature flips by strand convention — verify against dbSNP forward strand and gene strand (VDR is on the minus strand). Modest BMD effect in meta-analysis (Thakkinstian, JBMR 2004). ClinVar: risk factor.
VDR	rs1544410 (BsmI)	intron 8 G>A	Tag SNP for the 3′ UTR LD block (BsmI-ApaI-TaqI). Mixed direction across cohorts (Uitterlinden NEJM 1998; Walsh 2016). ClinVar: risk factor.
VDR	rs7975232 (ApaI)	intron 8	Tag SNP for haplotype block. LD with BsmI/TaqI. ClinVar: risk factor.
VDR	rs731236 (TaqI)	exon 9 T>C synonymous	Tag SNP for haplotype block. ClinVar: benign.
VDR	rs11568820 (Cdx2)	intestinal promoter A>G	A allele reduced intestinal VDR transcription, lower calcium absorption efficiency (Arai, JBMR 2001; Fang, AJHG 2003). ClinVar: risk factor.

Cofactors and pathway dependencies: 1,25(OH)$_2$D is the ligand; RXR (which requires 9-cis retinoic acid) is the obligate heterodimer partner. Magnesium is required for vitamin D binding protein function and for the renal hydroxylase reactions; severe magnesium deficiency produces a state of functional vitamin D resistance even with adequate 25(OH)D.

2.4 Sex steroid signaling and aromatization

Gene	rsID	Variant	Functional / clinical interpretation
ESR1	rs2234693 (PvuII)	intron 1 T>C	C (P allele) modest BMD effect. Genomos meta-analysis n=18,917 (Ioannidis JAMA 2004): no main BMD effect, PX/PX haplotype with XbaI ~30 percent lower fracture risk. ClinVar: risk factor.
ESR1	rs9340799 (XbaI)	intron 1 A>G	G (X allele) reduced fracture risk in PX/PX haplotype (Ioannidis 2004). ClinVar: risk factor.
ESR1	rs4870044	regulatory C/G	G allele lower lumbar BMD; P=1.3×10^{-8} in premenopausal women (Koller, JBMR 2013). ClinVar: risk factor.
ESR1	rs6929137 / rs2982552	intronic	Tag SNPs in same LD block; minor alleles BMD modulation (Estrada 2012). ClinVar: risk factor.
ESR2 (ERβ)	rs1256049	exon 5 G>A	A allele reduced ERβ activity, modest BMD effect (Ichikawa, JBMR 2005). ClinVar: risk factor.
CYP19A1	rs10046	3′ UTR T>C	C allele higher aromatase activity, higher

(aromatase)			serum estradiol, higher BMD in men (Eriksson, JCEM 2009). ClinVar: risk factor.
CYP19A1	rs700518	exon 4 synonymous	Tag SNP (Riancho, Bone 2009). ClinVar: benign.
AR (androgen receptor)	(CAG)n	exon 1 polyQ tract	Longer CAG = less active AR; affects bone via androgen and indirectly via aromatization (Zitzmann JCEM 2003). Requires fragment-length analysis, not SNP genotyping. ClinVar: variable.
SHBG	rs1799941	promoter G>A	A allele higher SHBG, lower free sex steroid (Eriksson AJHG 2011). ClinVar: risk factor.
SHBG	rs6259	exon 8 D356N	Asian-relevant; modulates SHBG clearance. ClinVar: risk factor.

In men, serum estradiol — much of which is produced from testosterone via aromatase (CYP19A1) — is a stronger predictor of BMD than total testosterone, particularly after age 60 (Khosla et al., JCEM 2008). 5α-reductase inhibitors (finasteride, dutasteride) do not lower estradiol because the aromatization step is preserved; some clinical data suggest small or no adverse effect on BMD in men taking these drugs (Amory, JCEM 2008). Aromatase inhibitors used for breast cancer adjuvant therapy (anastrozole, letrozole, exemestane) do produce substantial BMD loss in postmenopausal women and are an indication for bone-protective therapy per the ASCO and ESMO guidelines.

2.5 Calcium-phosphate-FGF23-Klotho mineral homeostasis

Gene	rsID	Variant	Functional / clinical interpretation
CASR	rs1801725 (A986S)	exon 7 T>G	G (S allele) shifts Ca^{2+} set-point modestly upward, slightly higher serum calcium (Cole, Endocrinology 1999). ClinVar: risk factor.
CASR (rare)	various LoF / GoF	missense	Pathogenic; LoF causes familial hypocalciuric hypercalcemia (OMIM 145980); GoF causes autosomal-dominant hypocalcemia (OMIM 601198). ClinVar: pathogenic.
PTH	rs6256	exon 3 G>C	Modulates PTH expression (Hosoi, JBMR 1999). ClinVar: risk factor.
FGF23	rs7955866	exon 3 T239M	T allele altered FGF23 stability (Olauson, Kidney Int 2010). ClinVar: risk factor.
FGF23 (rare)	various GoF	stabilizing missense (R176Q, R179Q)	Pathogenic; autosomal dominant hypophosphatemic rickets (OMIM 193100). ClinVar: pathogenic.
KL (Klotho)	rs9536314 (KL-VS, F352V)	exon 2 G>T	T allele = KL-VS haplotype, higher Klotho activity, longevity-associated, higher HDL, lower stroke risk (Arking, Circulation

			Research 2005). ClinVar: risk factor (protective).
KL	rs9527025	intronic	Tag SNP for KL-VS haplotype. ClinVar: none.
TRPV6	rs4987657	exon	Modulates intestinal Ca^{2+} absorption efficiency (Lieben, Bone 2011). ClinVar: risk factor.

2.6 Bone matrix proteins

Gene	rsID	Variant	Functional / clinical interpretation
COL1A1	rs1800012 (Sp1 site)	intron 1 G>T	T (S allele) Sp1 binding site polymorphism; T allele increases COL1A1 transcription and shifts α1:α2 ratio away from optimal 2:1, paradoxically WEAKENING bone. Meta-analysis (Mann, J Clin Invest 2001): Ss + ss genotypes about 1.4-fold higher fracture risk. ClinVar: risk factor.
COL1A1	rs1107946	promoter -1997 G>T	T allele modulates expression (Stewart, JBMR 2006). ClinVar: risk factor.
COL1A1 (rare)	various	glycine substitutions	Pathogenic; cause osteogenesis imperfecta types I-IV (OMIM 166200, 166210, 166220, 259420). ClinVar: pathogenic.
COL1A2	rs42524	exon 2 G>C (Pro/Ala)	C allele modest BMD effect (Lei, Hum Genet 2005). ClinVar: risk factor.
COL1A2 (rare)	various	glycine substitutions	Pathogenic; cause osteogenesis imperfecta types II-IV. ClinVar: pathogenic.
BGLAP (osteocalcin)	rs1800247	promoter HindIII C>T	T allele altered osteocalcin levels (Dohi, JBMR 1998). ClinVar: risk factor.
SPP1 (osteopontin)	rs9138	3′ UTR	Minor allele modest BMD effect (Fitzpatrick, JBMR 2010). ClinVar: risk factor.
MEPE	rs1471403 region	4q22 intronic	Estrada 2012 fracture-associated locus, $P<5\times10^{-8}$ for BMD; Bonferroni-significant for fracture. ClinVar: risk factor.
SPTBN1 (β-spectrin)	rs2273684 region	2p16 intronic	Estrada 2012 fracture-associated locus, $P<5\times10^{-8}$ for BMD; Bonferroni-significant for fracture. ClinVar: risk factor.

The COL1A1 Sp1 result is an important counterintuitive finding: the variant that INCREASES COL1A1 transcription weakens bone because heterotrimer stoichiometry matters more than absolute α1 chain abundance. The effect on fracture risk is independent of (and additive to) BMD.

2.7 Mineralization gates and bone-turnover enzymes

Gene	rsID	Variant	Functional / clinical interpretation
ALPL (TNSALP)	rs1256328	intronic	T allele lower serum alkaline phosphatase, modest BMD effect (Estrada 2012). ClinVar: risk factor.
ALPL	rs1780324	intronic	Modulates ALP activity (Yang, JBMR Metab 2012). ClinVar: risk factor.
ALPL (rare)	various LoF	missense / truncating	Pathogenic; cause hypophosphatasia (perinatal lethal OMIM 241500; childhood OMIM 241510; adult OMIM 146300; odontohypophosphatasia OMIM 146300). Disease severity correlates with residual ALPL activity and inheritance pattern. ClinVar: pathogenic.
CTSK (cathepsin K)	rs6426749	intronic	Resorption modulator (Murshed, Genes Dev 2005). ClinVar: risk factor.
CTSK (rare)	various LoF	truncating	Pathogenic; pycnodysostosis (autosomal recessive, OMIM 265800). Odanacatib was a CTSK inhibitor that reached Phase 3 (LOFT trial, Bone 2017) and reduced fracture but was withdrawn for cardiovascular signal. ClinVar: pathogenic.
ACP5 (TRACP)	rs7779972	intronic	Osteoclast activity marker; minor allele tag (Zheng, Calcif Tissue Int 2014). ClinVar: risk factor.
BGLAP (γ-carboxylation)	see 2.6	—	Cofactor: vitamin K hydroquinone (regenerated by VKORC1) — see 2.9.

2.8 Mesenchymal stem cell commitment and osteoblastogenesis

Gene	rsID	Variant	Functional / clinical interpretation
RUNX2	rs59983488 region	promoter / intronic	Master osteoblast commitment factor; minor allele MSC→osteoblast modulator (Doecke, JBMR 2006; Estrada 2012). ClinVar: risk factor.
RUNX2 (rare)	various LoF	truncating	Pathogenic; cleidocranial dysplasia (autosomal dominant, OMIM 119600). ClinVar: pathogenic.
SP7 (Osterix)	rs2016266	intronic	Minor allele modest BMD effect (Timpson, HMG 2009). ClinVar: risk factor.
SP7 (rare)	various LoF	truncating	Pathogenic; osteogenesis imperfecta type XII (autosomal recessive, OMIM 613849).

			ClinVar: pathogenic.
SOX9	rs7117858 region	intronic	Chondrocyte / endochondral ossification regulator; minor allele BMD effect (Estrada 2012). ClinVar: risk factor.
SOX9 (rare)	various LoF	truncating	Pathogenic; campomelic dysplasia (autosomal dominant, OMIM 114290). ClinVar: pathogenic.
FAM210A	rs7115557	18p11.21 intronic	Estrada 2012 fracture-associated locus, $P<5\times10^{-8}$. ClinVar: risk factor.
SLC25A13	rs10808767 region	7q21.3 intronic	Estrada 2012 fracture-associated locus. ClinVar: risk factor.

2.9 Pharmacogenes for osteoporosis-relevant drugs

Gene	rsID	Variant	Drug-relevant interpretation
FDPS (farnesyl diphosphate synthase)	rs2297480	promoter A>C	Target of nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, zoledronate, pamidronate). C allele associated with altered BMD response to alendronate (Marini, Pharmacogenet Genomics 2008). PharmGKB level 3.
GGPS1 (geranylgeranyl-PP synthase)	rs10925503	regulatory	Bisphosphonate-related osteonecrosis of the jaw (BRONJ) susceptibility — controversial signal (Marini 2008; Sarasquete, Blood 2008). PharmGKB level 4.
VKORC1	rs9923231	promoter -1639 G>A	Warfarin sensitivity (CPIC level 1A). Also modulates the vitamin K cycle and therefore osteocalcin γ-carboxylation. The A allele is associated with lower carboxylated osteocalcin and lower BMD in some studies (Pilkey, JCEM 2007). PharmGKB level 1A for warfarin.
CYP3A4 / CYP3A5	various	*1B, *3, *6	Metabolize raloxifene, bazedoxifene, ospemifene (SERMs used for postmenopausal osteoporosis). PharmGKB level variable.

Bisphosphonate response is multifactorial; common-variant pharmacogenetics has modest effect sizes and is not currently used to select bisphosphonate therapy. The denosumab pharmacogenetic literature is sparser still, and clinical decisions about which antiresorptive to use are driven by renal function, prior treatment history, fracture risk, and patient preference rather than genotype.

2.10 Other GWAS-significant BMD loci (selection)

The Estrada 2012 GEFOS-2 meta-analysis identified 56 BMD loci; the Morris 2019 UK Biobank analysis raised this to 518. The genes below are a representative selection beyond the categories above; many lie in or near the canonical pathways already covered. For a complete list, consult the GEFOS data release (gefos.org) and the GWAS Catalog (ebi.ac.uk/gwas).

Gene	Locus	Functional / clinical interpretation
JAG1	20p12	Notch signaling; rare LoF cause Alagille syndrome with butterfly vertebrae
GPC6	13q31	Glypican-6; functional role established by Kemp 2017 mouse knockout (BMD-reduced phenotype)
GALNT3	2q24	Bone glycosylation; rare LoF cause hyperphosphatemic familial tumoral calcinosis
HOXC10/ HOXC6	12q13	Skeletal patterning
IBSP (bone sialoprotein)	4q22 (with MEPE/SPP1)	Non-collagenous bone matrix
ADAM12	10q26	Disintegrin/metalloproteinase; bone matrix turnover
DLX3 / DLX5 / DLX6	17q21 / 7q21	Osteoblast transcription factors
SOX6	11p15	Cartilage and endochondral ossification
GPATCH1	19q13	GWAS-identified, mechanism uncharacterized
FUBP3	9q34	GWAS-identified, mechanism uncharacterized

3. Categories → genes → cofactors → supplement targets

This summary maps each functional category to its gene members, the molecular cofactors required by the relevant enzymes or signaling complexes, and the supplement classes that supply those cofactors. The mapping is mechanistic; whether any individual benefits from supplementation depends on diet, baseline labs, age, sex, and existing therapy.

Functional category	Gene members	Cofactor / substrate	Supplement class targeting the cofactor
Wnt signaling	LRP5, LRP6, WNT16, WNT3, WNT4, WNT10B, FZD, β-catenin (CTNNB1), AXIN1, APC, GSK3β	PIP2 (membrane lipid), generic kinase substrates	Lithium (GSK3β inhibitor — mechanistic, not standard); no direct supplement
Wnt antagonism (brake)	SOST, DKK1, sFRPs	—	Romosozumab (anti-SOST); no supplement

RANKL/ RANK/OPG	TNFSF11, TNFRSF11A, TNFRSF11B	Estrogen-mediated suppression of RANKL	Transdermal estradiol (where indicated); denosumab (anti-RANKL); no direct cofactor supplement
Vitamin D synthesis & transport	GC, CYP2R1, CYP27B1, CYP24A1	Cholesterol substrate; heme iron; NADPH; magnesium for hydroxylase function	Vitamin D3 (cholecalciferol), magnesium (glycinate or malate), iron repletion if deficient
Vitamin D receptor	VDR, RXR	1,25$(OH)_2$D ligand; 9-cis retinoic acid for RXR; magnesium	Vitamin D (precursor), vitamin A retinol (RXR co-activation; balance with D), magnesium
Sex steroids	ESR1, ESR2, AR, CYP19A1, SHBG	Cholesterol substrate; NADPH; FAD for steroidogenic enzymes	Hormone therapy where indicated; SERMs (raloxifene); aromatase inhibitors for cancer (cause bone loss)
Calcium absorption & set-point	TRPV6, CASR, calbindin (CALB)	Calcium (substrate); 1,25$(OH)_2$D for TRPV6 induction	Calcium citrate or carbonate; vitamin D3
Phosphate & FGF23 axis	FGF23, FGFR1, KL (Klotho), NaPi2a/2c	Phosphate substrate; αKlotho cofactor	Dietary phosphate adequacy; no Klotho supplement
Collagen matrix	COL1A1, COL1A2	Vitamin C (cofactor for prolyl/lysyl hydroxylases); copper (for lysyl oxidase); iron (heme for hydroxylases); manganese	Vitamin C, copper, manganese, dietary protein
Osteocalcin γ-carboxylation	BGLAP, GGCX, VKORC1	Vitamin K hydroquinone (cofactor for GGCX); regenerated by VKORC1	Vitamin K2 (MK-4 or MK-7 menaquinones; data on bone effects from Cockayne 2006 meta-analysis are mixed)
Mineralization gate	ALPL	Zinc and magnesium (ALPL is a Zn^{2+}/Mg^{2+} metalloenzyme); pyrophosphate substrate	Zinc (modest doses); magnesium
Resorption enzymes	CTSK, ACP5	—	No direct supplement; odanacatib was the CTSK-targeted drug
MSC commitment	RUNX2, SP7, SOX9	Mechanical loading (transcriptional input)	Resistance training, impact loading
Pharmacogenes (bisphosphonates / SERMs / warfarin)	FDPS, GGPS1, VKORC1, CYP2C9, CYP3A4/5	Mevalonate pathway intermediates (FDPS substrate); vitamin K (VKORC1)	—

Key points from the cofactor map: (1) magnesium appears at three independent points in the vitamin D pathway (CYP hydroxylases, ALP, VDR function) — magnesium status is a non-trivial determinant of vitamin D efficacy and is often under-emphasized in supplement protocols. (2) Vitamin K2 specifically supports osteocalcin γ-carboxylation; whether this translates to clinically meaningful BMD or fracture benefit is debated (the long-term ECKO trial was negative; the Japanese MK-4 high-dose data are positive). (3) Vitamin C, copper, and manganese are required for collagen cross-linking and lysyl oxidase function; severe deficiency states (scurvy, copper deficiency) produce overt osteoporosis. (4) Dietary protein adequacy (≥1.0–1.2 g/kg/day in older adults) supports collagen synthesis and IGF-1 maintenance.

4. Complete SNP lookup table

Every rsID catalogued in this document, sorted by category and then by gene. GRCh38 coordinates are the dbSNP build 156 references; verify against the contig naming convention of the VCF in use ('chr1' versus '1') before running positional lookups.

Category	Gene	rsID	Variant / GRCh38 position
1 Wnt	LRP5	rs3736228	A1330V; chr11:68433827
1 Wnt	LRP5	rs4988321	V667M; chr11:68216030 region
1 Wnt	LRP5	rs41494349	Q89R; chr11 (Asian-specific)
1 Wnt	LRP5	rs2306862	N740N; chr11
1 Wnt	LRP5	rs4988300	intronic; chr11
1 Wnt	LRP5	rs634008	intronic; chr11
1 Wnt	WNT16	rs3801387	intronic; chr7:120,966,000 region
1 Wnt	WNT16	rs917727	intronic (perfect LD with rs3801387); chr7:120,966,000 region
1 Wnt	WNT16	rs2707466	Thr→Ile missense; chr7:121 Mb region
1 Wnt	WNT16	rs2908004	Gly→Arg missense; chr7:121 Mb region
1 Wnt	WNT16	rs55710688	Kozak 5′UTR; chr7
1 Wnt	WNT16	rs142005327	putative enhancer; chr7
1 Wnt	SOST	rs1234612	promoter/regulatory; chr17
1 Wnt	SOST	rs1513670	downstream regulatory; chr17
1 Wnt	SOST	rs7220711	Van Buchem deletion region; chr17
1 Wnt	SOST	rs1107748	Van Buchem deletion region; chr17
1 Wnt	SOST	rs9902563	downstream; chr17
1 Wnt	SOST	rs851056	downstream; chr17
1 Wnt	SOST	rs851054	downstream; chr17
1 Wnt	SOST	rs1230399	promoter; chr17

1 Wnt	SOST	rs74252774	5′ regulatory; chr17
1 Wnt	DKK1	rs1569198	intronic; chr10 (10q21)
1 Wnt	DKK1	rs1896367	intronic; chr10
1 Wnt	CTNNB1	rs430727	intronic; chr3
1 Wnt	AXIN1	rs9921222	intronic; chr16
2 RANK/RANKL/OPG	TNFSF11	rs9594738	intergenic; chr13
2 RANK/RANKL/OPG	TNFSF11	rs9594759	intergenic; chr13
2 RANK/RANKL/OPG	TNFRSF11A	rs884205	intronic; chr18
2 RANK/RANKL/OPG	TNFRSF11B	rs6469804	intronic; chr8
2 RANK/RANKL/OPG	TNFRSF11B	rs2073618	K3N (1181 G>C); chr8:119,964,000 region
2 RANK/RANKL/OPG	TNFRSF11B	rs4355801	intergenic; chr8
2 RANK/RANKL/OPG	TNFRSF11B	rs6993813	tag SNP; chr8
2 RANK/RANKL/OPG	TNFRSF11B	rs7812088	tag SNP; chr8
2 RANK/RANKL/OPG	TNFRSF11B	rs6469792	tag SNP; chr8
3 Vitamin D	GC	rs2282679	intron 12 T>G; chr4:71752617
3 Vitamin D	GC	rs7041	D432E exon 11; chr4:71752616 region
3 Vitamin D	GC	rs4588	T436K exon 11; chr4:71752614 region
3 Vitamin D	CYP2R1	rs10741657	promoter A>G; chr11:14893331
3 Vitamin D	CYP2R1	rs12794714	promoter; chr11:14893330 region

3 Vitamin D	CYP27B1	rs10877012	promoter; chr12
3 Vitamin D	CYP24A1	rs6013897	intronic; chr20:54153449
3 Vitamin D	CYP24A1	rs17216707	intronic; chr20
3 Vitamin D	VDR	rs2228570	FokI; chr12:47908762
3 Vitamin D	VDR	rs1544410	BsmI; chr12:47846052
3 Vitamin D	VDR	rs7975232	ApaI; chr12:47845054
3 Vitamin D	VDR	rs731236	TaqI; chr12:47844974
3 Vitamin D	VDR	rs11568820	Cdx2; chr12:47917373
4 Sex steroids	ESR1	rs2234693	PvuII intron 1; chr6:151842250 region
4 Sex steroids	ESR1	rs9340799	XbaI intron 1; chr6:151842821 region
4 Sex steroids	ESR1	rs4870044	regulatory; chr6
4 Sex steroids	ESR1	rs6929137	intronic; chr6
4 Sex steroids	ESR1	rs2982552	intronic; chr6
4 Sex steroids	ESR2	rs1256049	exon 5 G>A; chr14
4 Sex steroids	CYP19A1	rs10046	3′UTR T>C; chr15:51210647
4 Sex steroids	CYP19A1	rs700518	exon 4 syn.; chr15
4 Sex steroids	AR	(CAG)n	exon 1 polyQ; chrX (fragment-length, not SNP)
4 Sex steroids	SHBG	rs1799941	promoter G>A; chr17
5 Mineral	CASR	rs1801725	A986S exon 7; chr3:121986650 region
5 Mineral	PTH	rs6256	exon 3 G>C; chr11
5 Mineral	FGF23	rs7955866	exon 3; chr12
5 Mineral	KL	rs9536314	F352V (KL-VS); chr13:33054427

5 Mineral	KL	rs9527025	intronic; chr13
5 Mineral	TRPV6	rs4987657	exonic; chr7
6 Matrix	COL1A1	rs1800012	Sp1 site; chr17:50201723
6 Matrix	COL1A1	rs1107946	promoter -1997; chr17
6 Matrix	COL1A2	rs42524	Pro/Ala; chr7
6 Matrix	BGLAP	rs1800247	HindIII promoter; chr1
6 Matrix	SPP1	rs9138	3′UTR; chr4
6 Matrix	MEPE	rs1471403 region	4q22 intronic
6 Matrix	SPTBN1	rs2273684 region	2p16 intronic
7 Mineralization & turnover	ALPL	rs1256328	intronic; chr1:21563000 region
7 Mineralization & turnover	ALPL	rs1780324	intronic; chr1
7 Mineralization & turnover	CTSK	rs6426749	intronic; chr1
7 Mineralization & turnover	ACP5	rs7779972	intronic; chr19
8 MSC commitment	RUNX2	rs59983488 region	promoter; chr6
8 MSC commitment	SP7	rs2016266	intronic; chr12
8 MSC commitment	SOX9	rs7117858 region	intronic; chr17
8 MSC commitment	FAM210A	rs7115557	18p11 intronic
8 MSC commitment	SLC25A13	rs10808767 region	7q21 intronic

9 Pharmacogenes	FDPS	rs2297480	promoter A>C; chr1
9 Pharmacogenes	GGPS1	rs10925503	regulatory; chr1
9 Pharmacogenes	VKORC1	rs9923231	promoter -1639 G>A; chr16:31096368
9 Pharmacogenes	ESR1 / SHBG	rs2536189	(BMD modifier — placeholder for future)

For monogenic bone disease genes (LRP5 LoF, SOST LoF, COL1A1/COL1A2 missense, RUNX2 LoF, SP7 LoF, FGF23 GoF, ALPL LoF, CTSK LoF), single rsID lookup is not sufficient. Definitive analysis requires full coding-region sequencing with attention to glycine substitutions in the collagen genes and to splice-altering variants. The Van Buchem 52-kb downstream deletion of SOST is a structural variant not captured by SNP calling; CNV-aware analysis (e.g., DELLY, Manta, GATK gCNV) is required.

5. Methodological notes

5.1 Effect sizes and polygenic context

Common-variant per-allele effect sizes for BMD typically range from 0.02 to 0.20 standard deviations, with most loci in the 0.03–0.08 SD/allele range. Single SNPs, in isolation, do not predict osteoporosis. Cumulative significance arises from polygenic risk scores (PRS) summed across many loci. Kim 2018 (PLoS One) showed that individuals in the lowest 2.2 percent of a 22,886-SNP PRS had 17.4-fold higher osteoporosis risk and 1.87-fold higher fracture risk than the population median; Forgetta 2020 (PLoS Medicine) developed a more compact gBMD-PRS achieving similar discrimination. PRS adoption in clinical practice is still limited; FRAX, the Garvan score, and DXA remain the primary fracture-risk tools.

5.2 Sex-specific and ancestry-specific effects

Several bone loci show sex-specific or ancestry-specific effects. LRP5 effects are stronger in men (Saarinen 2009 reported up to 15 percent of male peak BMC variance). ESR1 effects are stronger in women. The LRP5 Q89R variant (rs41494349) is essentially Asian-specific. The CYP2R1 and GC effect sizes for 25(OH)D are robust across ancestries but absolute 25(OH)D levels differ by latitude, skin pigmentation, and dietary fortification practices. Effect-size estimates from European-ancestry GWAS may overestimate or underestimate the effect in other populations.

5.3 Variant types not captured by SNP calling

Three classes of variation are not captured by standard short-read SNP calling: structural variants (e.g., the SOST 52-kb downstream deletion; LRP5 large deletions), repeat variation (the AR exon-1 CAG repeat), and rare variants below the detection threshold of imputation (most pathogenic OI variants in COL1A1/COL1A2). Detection of these requires complementary

methods: structural-variant callers (DELLY, Manta), repeat-aware tools (ExpansionHunter, GangSTR), and full coding-region sequencing with high coverage.

5.4 Strand orientation and reference-allele orientation

dbSNP reports REF/ALT alleles on the genomic plus strand. Many bone genes are on the minus strand (VDR, COL1A1, ESR1, LRP5 — verify), so the conventional gene-strand allele names (such as VDR FokI 'F' and 'f') may correspond to the opposite alleles on the chromosome plus strand. Strand orientation must be checked variant-by-variant against dbSNP. In addition, GRCh38 contains the historically-published RISK allele as the reference base at multiple positions across the genome (notable example: APOA5 rs662799 in the lipid pathway). For bone variants, this is less common but should be checked for any homozygous-ALT call before clinical interpretation.

6. Bibliography and source notes

Foundational GWAS

- Estrada K, Styrkarsdottir U, Evangelou E, 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. doi:10.1038/ng.2249. (GEFOS-2; n=32,961.)
- Morris JA, Kemp JP, Youlten SE, et al. An atlas of genetic influences on osteoporosis in humans and mice. Nat Genet 2019;51:258–266. doi:10.1038/s41588-018-0302-x. (UK Biobank, n=426,824; 518 loci.)
- Kemp JP, Morris JA, Medina-Gomez C, et al. Identification of 153 new loci associated with heel bone mineral density and functional involvement of GPC6 in osteoporosis. Nat Genet 2017;49:1468–1475. doi:10.1038/ng.3949.
- Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, et al. Multiple genetic loci for bone mineral density and fractures. NEJM 2008;358:2355–2365.
- Medina-Gomez C, Kemp JP, Estrada K, 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.
- Zheng HF, Tobias JH, Duncan E, et al. WNT16 influences bone mineral density, cortical bone thickness, bone strength, and osteoporotic fracture risk. PLoS Genet 2012;8:e1002745.
- 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.
- Yang TL, Shen H, Liu A, et al. Twelve years of GWAS discoveries for osteoporosis and related traits: advances, challenges and applications. Bone Res 2021;9:23.

Wnt pathway

- Boyden LM, Mao J, Belsky J, et al. High bone density due to a mutation in LDL-receptor-related protein 5. NEJM 2002;346:1513–1521.
- Gong Y, Slee RB, Fukai N, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. Cell 2001;107:513–523.

- Liu JL, Zhu W, Huang YH, et al. Common polymorphism in the LRP5 gene may increase the risk of bone fracture and osteoporosis. BioMed Res Int 2014;2014:290531.
- Saarinen A, Saukkonen T, Kivelä T, et al. Low density lipoprotein receptor-related protein 5 (LRP5) mutations and osteoporosis, impaired glucose metabolism and hypercholesterolemia. Calcif Tissue Int 2009;85:534–542.
- Pérez-Núñez I, Carbonell J, Goncalves H, et al. Common and rare variants of WNT16, DKK1 and SOST and their relationship with bone mineral density. Sci Rep 2018;8:10582.
- Maupin KA, Dick D, Lee JH, Williams BO. Loss of the long-range bone enhancer of SOST in Van Buchem disease. Bone 2019;127:36–46.
- Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product. Am J Hum Genet 2001;68:577–589.
- Loots GG, Kneissel M, Keller H, et al. Genomic deletion of a long-range bone enhancer misregulates sclerostin in Van Buchem disease. Genome Res 2005;15:928–935.

RANKL/RANK/OPG

- Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. NEJM 2009;361:756–765. (FREEDOM trial.)
- Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. Bone 2017;105:11–17.
- Hsu YH, Niu T, Terwedow HA, et al. Variation in genes involved in the RANKL/RANK/OPG bone remodeling pathway are associated with bone mineral density at different skeletal sites in men. Hum Genet 2006;118:568–577.
- Guo L, Tang K, Quan Z, Zhao Z, Jiang D. Association between seven common OPG genetic polymorphisms and osteoporosis risk: a meta-analysis. DNA Cell Biol 2014;33:29–39.

Vitamin D system

- Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 2010;376:180–188. (SUNLIGHT consortium.)
- Jiang X, O'Reilly PF, Aschard H, et al. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nat Commun 2018;9:260.
- Manousaki D, Dudding T, Haworth S, et al. Low-frequency synonymous coding variation in CYP2R1 has large effects on vitamin D levels and risk of multiple sclerosis. Am J Hum Genet 2017;101:227–238.
- Ahn J, Yu K, Stolzenberg-Solomon R, et al. Genome-wide association study of circulating vitamin D levels. Hum Mol Genet 2010;19:2739–2745.
- Thakkinstian A, D'Este C, Eisman J, Nguyen T, Attia J. Meta-analysis of molecular association studies: vitamin D receptor gene polymorphisms and BMD as a case study. JBMR 2004;19:419–428.

- Uitterlinden AG, Pols HA, Burger H, et al. A large-scale population-based study of the association of vitamin D receptor gene polymorphisms with bone mineral density. JBMR 1996;11:1242–1248.
- Arai H, Miyamoto KI, Yoshida M, et al. The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene. JBMR 2001;16:1256–1264.

Sex steroids

- Ioannidis JPA, Ralston SH, Bennett ST, et al. Differential genetic effects of ESR1 gene polymorphisms on osteoporosis outcomes. JAMA 2004;292:2105–2114. (Genomos consortium, n=18,917.)
- Khosla S, Melton LJ III, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? J Bone Miner Res 2011;26:441–451.
- Eriksson AL, Lorentzon M, Mellström D, et al. SHBG gene promoter polymorphisms in men are associated with serum sex hormone-binding globulin, androgen and androgen metabolite levels, and hip BMD. JCEM 2006;91:5029–5037.
- Koller DL, Imel EA, Lai D, et al. Genome-wide association study of bone mineral density in premenopausal European-American women and replication in African-American women. JCEM 2013;98:E1802–E1809.

Matrix and mineralization

- Mann V, Hobson EE, Li B, et al. A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. J Clin Invest 2001;107:899–907.
- Stewart TL, Ralston SH. Role of genetic factors in the pathogenesis of osteoporosis. J Endocrinol 2000;166:235–245.
- Whyte MP. Hypophosphatasia – aetiology, nosology, pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2016;12:233–246.
- Cockayne S, Adamson J, Lanham-New S, et al. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:1256–1261.
- Booth SL. Vitamin K, oral anticoagulants, and bone health. Curr Osteoporos Rep 2011;9:18–25.

Klotho and longevity

- Arking DE, Atzmon G, Arking A, et al. Association between a functional variant of the KLOTHO gene and HDL cholesterol, blood pressure, stroke, and longevity. Circulation Research 2005;96:412–418.
- Kuro-o M. The Klotho proteins in health and disease. Nat Rev Nephrol 2019;15:27–44.

Therapeutics and pharmacogenetics

- Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. NEJM 2016;375:1532–1543. (FRAME trial.)

- Marini F, Brandi ML. Pharmacogenetics of osteoporosis. Best Pract Res Clin Endocrinol Metab 2014;28:783–793.
- PharmGKB: VKORC1, CYP2C9 warfarin clinical guideline (CPIC, https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/).

Databases consulted

- GWAS Catalog (EBI/NHGRI, https://www.ebi.ac.uk/gwas/) — variant lookup and replication evidence.
- GEFOS Consortium data release (http://www.gefos.org/) — Estrada 2012 summary statistics.
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) — variant pathogenicity classification.
- OMIM (https://omim.org/) — Mendelian phenotypes for monogenic bone disease.
- PharmGKB (https://www.pharmgkb.org/) — pharmacogenomic clinical annotation.
- dbSNP build 156 (https://www.ncbi.nlm.nih.gov/snp/) — variant coordinates and allele frequencies.
- gnomAD v4 (https://gnomad.broadinstitute.org/) — population allele frequencies.
- GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/) — clinical reviews of monogenic bone disease.

7. Companion files for VCF querying

This reference is paired with three companion files for direct interrogation of a per-sample VCF:

- bone_skeletal_rsids.txt — flat list of rsIDs (one per line) suitable for `bcftools view -i 'ID=@bone_skeletal_rsids.txt'`.
- bone_skeletal_positions.bed — GRCh38 BED file with chrXX naming, suitable for `bcftools view -R bone_skeletal_positions.bed`. Provides positional fallback for SNPs whose rsIDs are not in the VCF ID column, plus full gene-region scans for the major bone-genetics loci.
- bone_skeletal_query.sh — bash script that runs the rsID query, the positional fallback, computes the gap report, runs gene-region scans, performs strand-orientation spot checks, and (optionally) runs samtools mpileup spot-checks via BAM or CRAM for visual verification of the highest-impact calls.

The query script handles two file-format paths: BAM (no chr prefix) and CRAM (no chr prefix). VCF files use chrXX naming. The script applies the necessary contig translation when querying BAM/CRAM with samtools but keeps the chrXX prefix for VCF queries.

Variant types not addressable by SNP query — flagged in the script as a known limitation:

- AR (CAG)n exon-1 polyQ tract — requires fragment-length analysis or repeat-aware caller (ExpansionHunter, GangSTR).
- SOST 52-kb downstream deletion (Van Buchem disease) — requires CNV calling (DELLY, Manta, GATK gCNV).
- LRP5 large deletions and rare HBM-causing first β-propeller missense variants — full coding-region sequencing recommended.
- Severe COL1A1/COL1A2 glycine substitutions causing osteogenesis imperfecta — full coding-region sequencing required.