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Table 1. Inherited bone fragility syndromes

Gene	Sillence type/ syndrome name	Severity	Protein	Additional phenotypic details
Collagen molecule				
COL1A1	I-IV	Mild-lethal	Type 1 collagen α1 chain	High bone mass in C-propeptide cleavage site defects – gracile "shattered" bones[28] Caffey disease with defect at p.Arg1014Cys[29]
COL1A2	I-IV	Mild-lethal	Type 1 collagen α2 chain	High bone mass in C-propeptide cleavage site defects
Collagen folding				
CRTAP	III	Severe-lethal	Cartilage associated protein	Cole-Carpenter features reported in one case.[30]
LEPRE1	III	Severe-lethal	Prolyl-3-hydroxylase	
PPIB	III	Moderate-lethal	Cyclophilin B	
Collagen stability				
FKBP10	III	Moderate-severe	FKBP65; 65kD FK506-binding protein	Bruck syndrome (OI with contractures)[20,22]; Kuskokwim syndrome (contractures alone)[31]
PLOD2	Bruck syndrome	Moderate-severe	Lysyl hydroxylase 2	Contractures
SERPINH1	III	Severe	Heat Shock Protein 47	Pyloric stenosis, skin bullae, renal stones[32]
SPARC	III	Moderate-severe	Secreted protein, acidic, cysteine-rich; osteonectin	Notable sarcopenia[33]
Collagen processing/cleavage				
BMP1	III	Mild-moderate	Bone morphogenetic protein 1; tolloid	High bone mass, similar to C-propeptide cleavage defects, hyperosteoidosis, cardiac defects[34-37]
Wnt-signalling pathway				
WNT1	III	Mild-severe	Wingless-type MMTV integration site family, member 1	Homozygous – severe OI; some have brain malformation; autism, learning difficulties in some.[26,27] Heterozygous – early onset

				osteoporosis, normal growth
Mineralisation regulation				
IFITM5/ BRIL	V	Moderate - severe	Interferon-induced transmembrane protein 5, or, bone-restricted IFITM5-like	Metaphyseal dysplasia and sclerosis, hypertrophic callus, interosseous membrane calcification. [38-41]
SERPINF1	III	Moderate -severe	Pigment epithelium derived factor	Slowly progressively worsening OI; osteoid mineralization defect (no endochondral defect)[42]
Osteoblast lineage				
SP7/OSX	III	Severe	Specificity Protein 7; Osterix	Typical OI features[43]
Developmental/patterning				
TAPT1	III	Lethal	Transmembrane anterior posterior transformation-1 protein	Complex osteochondrodysplasia with multiple fractures; also have brain, cardio-respiratory and renal defects [44]
ER-related				
P4HB	III	Moderate -severe	Prolyl 4-hydroxylase; protein disulfide isomerase	Cole-Carpenter syndrome; craniosynostosis, ocular proptosis, hydrocephalus[23,25,45]
TMEM38B	III	Moderate -severe	Trimeric Intracellular Cation Channel Type B; TRIC-B	Severe osteopenia and limb fractures without vertebral fractures [46,47]
CREB3L1	III	Severe	Old Astrocyte Specifically Induced Substrate - OASIS	Severe OI; cardiac failure [48]
SEC24D	III	Moderate -severe	Component of COPII complex	Cole-Carpenter syndrome; craniosynostosis, ocular proptosis, hydrocephalus[24]
MBTPS2	III	Moderate -severe	Site-2 metalloproteinase S2P	regulated intramembrane proteolysis of transcription factors such as OASIS x-linked[49]
Nucleotidyltransferase fold protein				
FAM46A	III	Severe	Family with sequence similarity 46A	Stüve-Wiedemann – like features, blue sclerae[50]
Linker enzyme deficiency				
XYLT2	III	Moderate -severe	Xylosyltransferase II	Vertebral fractures, cataracts, heart defects [51]

Bone fragility, not clearly OI				
LRP5/6	N/A	Mild-severe	Lipoprotein receptor-related protein 5/6	Homozygous – osteoporosis pseudoglioma syndrome; Heterozygous – osteoporosis and/or vitreoretinopathy [52-55]
NBAS	N/A	Moderate-severe	Neuroblastoma Amplified Sequence	Early onset osteoporosis, recurrent acute liver failure, developmental delay[56,57]
LIFR	Stüve-Wiedemann syndrome	Moderate-severe	Leukaemia inhibitory factor receptor	Long bone bowing, camptodactyly, hyperpyrexia, fractures later[58]
Osteocyte dysfunction				
PLS3	N/A	N/A	Plastin 3	X-linked early onset severe osteoporosis without other OI features[59,60]