Paget Disease of Bone — Comprehensive Disease Characteristics Report

Disease: Paget Disease of Bone (PDB; osteitis deformans) **Category:** Metabolic Bone Disorder **Primary identifiers:** MONDO:0005479 · OMIM #167250 (PDB2, SQSTM1) / #602080 (PDB3) / #616833 (PDB6, ZNF687) · Orphanet ORPHA:2801 · ICD-10 M88 · ICD-11 FB80.0 · MeSH D010001 (Osteitis Deformans) **Evidence base:** 9 confirmed findings, 39 primary papers reviewed across 5 iterations. Evidence is drawn from aggregated disease-level resources (OMIM, Orphanet, GWAS meta-analyses, guideline statements), human clinical cohorts and registries, knock-in mouse models, and in-vitro osteoclast studies.

Summary

Paget disease of bone (PDB) is a chronic, focal, adult-onset metabolic bone disorder in which giant, hyperactive, hypernucleated osteoclasts drive intense localized bone resorption. This is followed by a disorganized compensatory increase in osteoblastic bone formation, producing expanded, structurally weak, hypervascular "mosaic" bone (mixed woven and lamellar). Clinically this manifests as bone pain, deformity, secondary osteoarthritis, pathological fracture, deafness (when the skull is involved), and — rarely (~0.7–1%) — malignant transformation to osteosarcoma. Many patients are asymptomatic and are detected incidentally through an elevated serum alkaline phosphatase (ALP) or an X-ray taken for another reason.

PDB is best understood as a **complex gene–environment disorder that converges on the osteoclast RANK–RANKL–OPG signaling axis and p62/autophagy machinery**. Mutations affecting the ubiquitin-associated (UBA) domain of **SQSTM1** (which encodes p62), especially the recurrent **p.P392L** variant, are the single most common genetic cause. Beyond SQSTM1, rarer causal genes (ZNF687, PFN1, VCP) and at least seven common susceptibility loci (CSF1, OPTN, TNFRSF11A/RANK, TM7SF4/DCSTAMP, PML, RIN3, NUP205) shape polygenic risk. A parallel, distinct recessive childhood disorder — **juvenile Paget's disease** — is caused chiefly by loss of osteoprotegerin (TNFRSF11B/OPG), directly confirming the centrality of the RANK–

RANKL–OPG axis. The steadily declining incidence and severity of PDB across multiple countries strongly implicates a diminishing environmental trigger whose identity remains unresolved.

Diagnosis rests on the combination of characteristic plain radiographs, an elevated serum ALP (the standard marker of disease activity), and a technetium-99m radionuclide bone scan to map disease extent. A **single 5-mg intravenous infusion of zoledronic acid** is first-line therapy and produces durable biochemical remission in ~90–97% of patients — far superior to older bisphosphonates — although a large randomized trial (PRISM-EZ) showed that intensively normalizing bone turnover does not improve fractures, pain, or quality of life versus symptomatic management. This report details all requested disease characteristics with primary-literature citations.

Section 1 — Disease Information

PDB is a chronic focal disorder of bone remodeling, the **second most common metabolic bone disease after osteoporosis** (PMID: 28690091). It is characterized by "increased osteoclast-mediated bone resorption and a subsequent compensatory increase in bone formation, resulting in a disorganized mosaic of woven and lamellar bone at one or more affected skeletal sites" (PMID: 30671590).

Key identifiers: MONDO:0005479; OMIM #167250 (classic SQSTM1-related PDB2), with additional loci PDB3 (#602080) and PDB6/ZNF687 (#616833); Orphanet ORPHA:2801; ICD-10 M88 (with subsite codes M88.0 skull, M88.8 other bones, M88.9 unspecified); ICD-11 FB80.0; MeSH D010001 (Osteitis Deformans).

Synonyms / alternative names: Osteitis deformans; Paget's disease of bone; Paget disease, bone; osteitis deformans of Paget. (Note: distinct from Paget disease of the breast/nipple and extramammary Paget disease, which are unrelated epithelial neoplasms.)

Information source type: Predominantly aggregated disease-level resources (OMIM, Orphanet, GWAS meta-analyses, guideline statements) supplemented by clinical cohorts, health-administrative databases (e.g., Quebec, UK), and disease registries. Some findings derive from individual-patient EHR/registry data (e.g., contemporary vs historical cohort comparisons; VCP CoRDS registry).

Section 2 — Etiology

Primary causal factors. PDB is a genetically heterogeneous disorder with a strong hereditary component overlaid on one or more environmental triggers. As reviewed, "PDB is a genetically heterogeneous disorder, with mutations in at least two different genes (SQSTM1, ZNF687) and more common predisposing variants," while "the focal nature of lesions, the decline in prevalence rates, and the incomplete penetrance of the disease among family members suggest that one or more environmental triggers may play a role" (PMID: 30671590).

Genetic risk factors. - **Causal:** SQSTM1 UBA-domain mutations (p.P392L most common) — present in ~10–40% of familial and ~5–10% of sporadic cases (Finding F001). Rarer causal genes: ZNF687 and PFN1 (severe, early-onset, polyostotic, giant-cell-tumor–prone forms) and VCP (syndromic PDB). - **Susceptibility loci:** Seven common GWAS loci — CSF1 (1p13), OPTN (10p13), TNFRSF11A/RANK (18q21), TM7SF4/DCSTAMP (rs2458413), PML (rs5742915), RIN3 (rs10498635), NUP205 (rs4294134) — together explaining ~13% of familial risk (Finding F006; PMID: 21623375).

Environmental risk factors. Age (incidence rises sharply after ~55 y), male sex, and family history are the principal established risk factors. Geographic and rural clustering suggests an environmental/zoonotic contribution: a Spanish study of 2,342 new cases found a moderate positive correlation between PDB incidence and density of female breeding cattle (R^2=0.236) (PMID: 40408225). A separate hypothesis links historical PDB prevalence to domestic bituminous coal burning (PMID: 38902530). The long-postulated chronic **paramyxovirus (measles) infection** of osteoclasts remains unconfirmed and contested (see Section 5).

Protective factors. No validated genetic protective variants or dietary/lifestyle protective factors are established. The declining incidence implies that **reduced exposure to the (unidentified) environmental trigger** is effectively protective at the population level (Finding F002).

Gene–environment interactions. The prevailing model holds that a genetic predisposition (e.g., SQSTM1/p62 UBA mutation or risk alleles at RANK/OPTN/CSF1/DCSTAMP) sensitizes osteoclast precursors, which then require an environmental "second hit" to produce focal lesions — explaining incomplete penetrance and the focal, localized nature of disease despite a germline mutation present in every cell (Findings F001, F009).

Section 3 — Phenotypes

Phenotype	Type	HPO term	Characteristics / frequency
Bone pain	Symptom	HP:0002653 (Bone pain)	Most common symptom; ~52% of symptomatic patients report pagetic bone pain in both historical and contemporary cohorts (PMID: 36858336); progressive/fluctuating
Bone deformity (bowing of long bones, skull enlargement)	Physical manifestation	HP:0002750 (Abnormal long bone morphology)	13% contemporary vs 54% historical cohort — declining severity (PMID: 36858336)
Pathological fracture	Clinical sign	HP:0002659 (Increased susceptibility to fractures)	6.7% contemporary vs 36.7% historical (PMID: 36858336)
Secondary osteoarthritis	Clinical sign	HP:0002758 (Osteoarthritis)	~43–52% of patients (PMID: 36858336)
Hearing impairment (skull involvement)	Clinical sign	HP:0000365 (Hearing impairment)	~52–61% when skull affected (PMID: 36858336)
Elevated serum alkaline phosphatase	Laboratory abnormality	HP:0003155 (Elevated circulating ALP)	Core biochemical hallmark; reflects disease activity/extent
Skull enlargement / cranial nerve compression	Physical manifestation	HP:0000256 (Macrocephaly); HP:0000365	Variable
Osteosarcoma (malignant transformation)	Clinical sign	HP:0002669 (Osteosarcoma)	Rare, ~0.7–1% (see Section 11)

Age of onset: adult/late-onset; typically diagnosed after age 55, mean age at diagnosis ~68.7 y in a contemporary cohort (PMID: 36858336). **Progression:** slowly progressive but focally stable; individual lesions expand over years. **Severity:** highly variable, ranging from asymptomatic incidental findings (~85% at diagnosis in contemporary series) to disabling deformity. **Quality-of-life impact:** driven mainly by chronic pain, deformity, secondary arthritis, and deafness; notably, the PRISM-EZ RCT found no QoL benefit from intensive bone-turnover suppression (PMID: 28176386).

Contemporary disease is milder: patients are older at diagnosis, more often monostotic (60.5%), with lower ALP, fewer pagetic bones, fewer fractures and deformities than historical cohorts (PMID: 36858336).

Section 4 — Genetic / Molecular Information

Causal genes. - **SQSTM1** (HGNC:11280; encodes p62/sequestosome-1; OMIM *601530) — the major gene. UBA-domain mutations, recurrent p.P392L (c.1175C>T), occur in ~10–40% of familial and ~5–10% of sporadic PDB and associate with more severe/extensive disease (PMID: 37180975; Finding F001). Functional consequence: impaired ubiquitin binding → dysregulated NF-κB signaling and autophagy → osteoclast hyperactivity. - ZNF687 (HGNC:13809) — causes severe, early-onset, polyostotic PDB with giant-cell tumor predisposition; variants cluster in the nuclear localization signal (e.g., p.Pro937Arg, p.Pro937His, p.Arg939Cys) (PMID: 37728743). - PFN1 (profilin-1) — very rare cause of severe PDB; essentially absent in most cohorts (PMID: 37728743). - VCP (p97; HGNC:12666) — autosomal-dominant missense mutations cause syndromic PDB within multisystem proteinopathy (see Section 6 & Finding F005). - TNFRSF11B/OPG, TNFRSF11A/RANK, SP7/osterix** — cause the distinct recessive juvenile Paget's disease (Finding F008).

Variant classification (ACMG/AMP): SQSTM1 p.P392L and other recurrent UBA-domain variants are classified pathogenic/likely pathogenic; ZNF687 NLS variants are supported as disease-associated (PMID: 37728743). Variant types are predominantly **missense**, with some truncating UBA-domain variants; large deletions dominate the most severe JPD phenotypes.

Somatic vs germline: Causal variants are **germline**. Somatic changes are relevant to the osteosarcomas that arise in pagetic bone (COSMIC-type analysis beyond present scope).

Modifier genes: The seven GWAS loci act as susceptibility/severity modifiers on top of SQSTM1; DCSTAMP, OPTN and CSF1 modulate osteoclast fusion and differentiation.

Epigenetic / chromosomal: No recurrent large-scale chromosomal abnormality defines classic PDB (JPD can involve large TNFRSF11B deletions). Systematic disease-specific methylation/ histone data were not identified in the reviewed literature — a knowledge gap.

Section 5 — Environmental Information

Environmental / occupational factors. Rural residence and proximity to livestock correlate with higher incidence (breeding-cattle density R^2=0.236) (PMID: 40408225). Historical domestic coal combustion has been proposed as a candidate exposure whose decline parallels falling PDB prevalence (PMID: 38902530).

Lifestyle factors. No robust smoking/diet/alcohol association is established; age and male sex remain the dominant demographic risk factors.

Infectious agents (contested). A chronic **paramyxovirus** infection of osteoclasts — variously measles virus (MV), respiratory syncytial virus (RSV), or canine distemper virus (CDV) — has been hypothesized for decades. Supporting: measles virus RNA was detected by in-situ hybridization in pagetic osteoclasts and other bone cells but not controls (PMID: 3701300). Refuting: PCR failed to detect paramyxovirus sequences in pagetic bone from 10 consecutive patients (PMID: 1805546); prior dog/cat ownership was not a risk factor in 433 US cases (PMID: 2376461); and a serological study of 463 patients found no elevation of MV/CDV/RSV antibodies (only a modest increase in mumps antibody) (PMID: 28361207). **Net assessment: the viral hypothesis remains unproven and is not currently supported by the weight of evidence.**

Section 6 — Mechanism / Pathophysiology

Central causal chain (Finding F009). Genetic predisposition (SQSTM1/p62 UBA mutation; risk alleles at TNFRSF11A/RANK, OPTN, CSF1, TM7SF4/DCSTAMP) + a putative environmental trigger → **osteoclast precursor hypersensitivity to RANKL** → dysregulated **NF-κB signaling** and **autophagy** (increased SQSTM1, ATG5, LC3-II) → formation of **giant, hypernucleated, hyperactive osteoclasts** with nuclear inclusions → focal intense **bone resorption** → compensatory **disorganized osteoblastic bone formation** (mixed woven + lamellar "mosaic" bone) → **expanded, weak, hypervascular** bone → pain, deformity, fracture, deafness, and rare osteosarcoma.

The osteoclast is the central effector: "the osteoclast, a myeloid-derived cell responsible for bone resorption, contributes to the disease" (PMID: 33768371). The P394L knock-in mouse confirms autophagy dysregulation downstream of the UBA mutation, with "increased expression of sqstm1, autophagy-related gene 5 (atg5) and light chain 3 gene (lc3) in osteoclast precursors" (PMID: 21515589).

Molecular pathways. RANK–RANKL–OPG (TNFRSF11A–TNFSF11–TNFRSF11B) axis; NF-κB signaling; ubiquitin–proteasome system and autophagy/lysosomal degradation (p62, VCP). GO suggestions: GO:0045672 (positive regulation of osteoclast differentiation), GO:0006914 (autophagy), GO:0043123 (positive regulation of canonical NF-κB signal transduction), GO:0045453 (bone resorption), GO:0002446 (neutrophil/myeloid-lineage regulation).

Protein dysfunction. p62 UBA-domain mutations impair ubiquitin binding, disrupting selective autophagy and NF-κB regulation. VCP/p97 is an AAA+ ATPase; "pathogenic mutations frequently found at the interface between the NTD domain and D1 ATPase domain … cause malfunction of VCP" (PMID: 38963497). MSP genes "share disruption of RNA stress granule function and autophagic degradation" (PMID: 33145792).

Cell types (CL): osteoclast (CL:0000092), osteoblast (CL:0000062), osteocyte (CL:0000137), osteoclast precursor / myeloid monocyte lineage. **Subcellular (GO CC):** autophagosome (GO:0005776), lysosome (GO:0005764), nucleus/nuclear inclusion bodies, cytoplasmic ubiquitin-rich inclusions.

Immune/inflammatory involvement. Osteoimmunology is central: RANKL-driven osteoclastogenesis is regulated by immune signaling; PDB is framed as an osteoclast-centric immunoskeletal disorder in "Osteoimmunology and Osteoclast Pathology" (PMID: 33768371).

Metabolic changes. High local bone turnover markedly elevates serum ALP and collagen breakdown products; systemic metabolic derangement is uncommon except high-output cardiac states in extensive polyostotic disease.

Section 7 — Anatomical Structures Affected

Organ/skeletal-site level. PDB is focal and can be monostotic or polyostotic. Commonly affected sites (UBERON): pelvis (UBERON:0001270), spine/vertebral column especially lumbar (UBERON:0001130), femur (UBERON:0000981), skull (UBERON:0000033), tibia (UBERON:0000979). Skull involvement causes cranial nerve compression and hearing loss;

spinal involvement can cause radiculopathy/myelopathy. The spine — particularly the lumbar spine — is a common site and a frequent location of malignant transformation (PMID: 42359209).

Secondary/system involvement. Cardiovascular (high-output state in extensive disease), nervous system (nerve/cord compression, deafness), joints (secondary osteoarthritis). **Tissue level:** bone/connective tissue; hypervascular marrow fibrosis. **Cell populations (CL):** osteoclasts (primary), osteoblasts, osteocytes.

Localization/laterality. Lesions are typically **asymmetric and focal**, may be unilateral or bilateral, and characteristically do not cross joint spaces; disease begins at one end of a long bone and advances along it (the radiographic "blade of grass"/flame-shaped front).

Section 8 — Temporal Development

Onset. Adult/late-onset, chronic, insidious; rarely diagnosed before age 40. Classic PDB is essentially never congenital (contrast juvenile Paget's disease, which presents in infancy/childhood — Section 9).

Progression. Individual lesions advance slowly and locally; overall the disease is chronic and lifelong but not systemically progressive in most patients. Stages within a lesion: an early **osteolytic/resorptive** phase → a **mixed** phase → a late **sclerotic/burnt-out** phase.

Patterns. Biochemical remission is **treatment-induced** (bisphosphonates); spontaneous remission of established lesions does not occur. The main "critical period" for intervention is symptomatic active disease with elevated ALP, where a single zoledronic acid infusion yields prolonged suppression (PMID: 31574000).

Section 9 — Inheritance and Population

Epidemiology. PDB is common in older adults of European descent but is **declining**. UK standardized incidence fell from 0.75/10,000 person-years (1999) to 0.20/10,000 (2015) (PMID: 33742666). In Quebec, standardized incidence fell from 0.77/1,000 (2000/01) to 0.28/1,000

(2019/20) while standardized prevalence stayed stable (~0.44% → 0.43%) (PMID: 37683713). Incidence rises steeply with age (UK crude incidence ≥85 y: 6.3/10,000 men, 3.7/10,000 women) and is higher in men.

Inheritance. Classic PDB is **complex/polygenic** with autosomal-dominant familial clustering in SQSTM1-linked families showing **incomplete, age-dependent penetrance** and **variable expressivity**. About 15–40% of patients have a family history. Seven common loci explain ~13% of familial risk (PMID: 21623375).

Juvenile Paget's disease (JPD; OMIM 239000) is a distinct **autosomal-recessive** disorder, most often from biallelic loss-of-function of **TNFRSF11B/OPG** — first shown as a homozygous deletion in Navajos (PMID: 32298837); the most severe phenotypes arise from "major gene deletions or mutations affecting cysteine residues in the ligand-binding domain" (PMID: 25108083). Heterozygous TNFRSF11A/RANK duplication and heterozygous SP7 mutation are rarer causes.

Population demographics. Highest prevalence historically in Britain and in populations of British descent (North America, Australia, New Zealand); largely absent in indigenous populations of those regions and low in Asia/Africa (PMID: 38902530). Male predominance (male:female ≈ 1.2–1.4:1). Founder effects operate in JPD (Navajo TNFRSF11B deletion).

Section 10 — Diagnostics

Recommended workup (Finding F007). Guidelines (Endocrine Society 2014; IOF/ASBMR/ECTS/UK Bone Research Society 2019) recommend **plain radiography + serum total alkaline phosphatase** for initial diagnosis and **technetium-99m radionuclide bone scintigraphy** to delineate extent (PMID: 32803929; PMID: 31574000).

- **Laboratory:** Elevated serum total ALP (bone-specific ALP if hepatic/pregnancy confounding); markers of bone turnover (P1NP, serum/urinary CTX, NTX) to assess activity and treatment response, typically remeasured at 3–6 months. Serum calcium usually normal.
- **Imaging:** X-ray shows cortical thickening, coarse trabeculation, bone expansion, osteoporosis circumscripta (skull), and the flame-shaped advancing lytic front in long bones. Bone scan identifies all active sites. CT/MRI is reserved for complications and suspected malignant transformation (PMID: 42359209).

- **Biopsy:** Not routinely required; reserved for atypical lesions or to exclude sarcoma. Histology shows the pathognomonic "mosaic" pattern with giant multinucleated osteoclasts.
- **Genetic testing:** SQSTM1 sequencing (single-gene / small panels including ZNF687, VCP, PFN1) is available but **not routine** — used mainly in early-onset, severe, or strongly familial disease and for research/cascade evaluation. WES/WGS have research utility for gene discovery.

Clinical criteria & differential diagnosis. Diagnosis is radiographic + biochemical. Differentials: osteoblastic metastases (esp. prostate/breast), primary bone tumors, sclerotic/lytic metabolic bone disease, fibrous dysplasia, and hyperparathyroidism.

Screening. No population screening is recommended. Because ALP elevation is often incidental, biochemical detection is common. Cascade genetic screening of relatives in SQSTM1 families is possible but not standard given incomplete penetrance and lack of proven benefit from early asymptomatic treatment.

Section 11 — Outcome / Prognosis

Overall prognosis is good for most patients; PDB is usually not life-limiting, and modern disease is milder. Prognosis "mainly depends on the occurrence of complications involving bones and joints, neurological, cardiovascular or metabolic systems" (PMID: 28690091).

Complications. Bone pain, deformity, secondary osteoarthritis, pathological fracture, deafness/cranial neuropathy, spinal stenosis, high-output cardiac failure (extensive disease), and — rarely — sarcomatous transformation.

Malignant transformation (Finding F004). Osteosarcoma occurs in ~0.7–1% of patients (historically up to ~5.5%). Contemporary incidence: "The incidence of malignant transformation was 0.7%, and the most frequent histologic type was osteogenic sarcoma" (PMID: 1451058). Tumors are mostly high-grade osteosarcomas (~88%), arise in older men (mean ~66 y), predominate in axial skeleton/pelvis and femur, and carry a dismal **~10% 5-year survival** (PMID: 17550323). Surgery ± chemotherapy offers the only realistic survival benefit but outcomes remain poor (PMID: 20652460; PMID: 42359209).

Prognostic factors. Extent/number of bones involved and baseline ALP correlate with disease burden; notably, sarcoma risk did **not** significantly correlate with number of bones involved or disease duration (PMID: 17550323). New/worsening pain, a soft-tissue mass, or a lytic lesion in known pagetic bone should prompt urgent evaluation for malignancy.

Section 12 — Treatment

First-line pharmacotherapy: intravenous bisphosphonates (NCIT: Zoledronic Acid; Bisphosphonate). A **single 5-mg IV zoledronic acid infusion** is standard first-line therapy and produces durable biochemical remission (Finding F003). It normalizes bone-turnover markers in the majority for ≥2 years independent of prior therapy (PMID: 17032148), and in head-to-head trials achieved therapeutic response in ~90–97% of patients versus ~45% for pamidronate (PMID: 17605632). Long-term durability: over 6.5 years without retreatment, relapse occurred in only 1/152 (0.7%) zoledronate vs 23/115 (20%) risedronate patients ($p<0.001$) (PMID: 21638319).

Regimen	Therapeutic response	Durability
Zoledronic acid 5 mg IV (single)	~90–97%	1/152 relapse at 6.5 y (PMID: 21638319)
Neridronate 200 mg (IV or IM)	92.6% (IV), 96.5% (IM) at 6 mo	Response declines by 24–36 mo (PMID: 20814970)
Pamidronate 30 mg IV	~45%	Inferior (PMID: 17605632)
Risedronate 30 mg PO	Lower	20% relapse at 6.5 y (PMID: 21638319)

Treatment goal — an important caveat. Despite superb biochemical control, the PRISM-EZ RCT (n=502) found that intensively normalizing bone turnover did **not** reduce fractures, orthopedic procedures, or bone pain, nor improve quality of life versus symptomatic treatment: "There were no clinically important differences in quality of life measures or bone pain between the treatment groups" (PMID: 28176386). Treatment is therefore aimed mainly at **symptom (pain) relief and protection of complication-prone sites**, not universal biochemical normalization.

Supportive care. Analgesics/NSAIDs for pain; calcium and vitamin D repletion before bisphosphonate dosing (response correlates with 25(OH)D — PMID: 20814970); physical therapy, hearing aids. **Surgery:** joint replacement for pagetic osteoarthritis, fracture fixation, osteotomy for deformity, decompression for neural compression; pre-operative bisphosphonate reduces hypervascular bleeding. **Experimental/advanced:** no gene, cell, or RNA therapy is approved for PDB. Adverse events of IV bisphosphonates: acute-phase reaction (~14%), hypocalcemia, and rare osteonecrosis of the jaw and atypical femoral fractures.

Section 13 — Prevention

- **Primary prevention:** None established, because the environmental trigger is unidentified. The natural population-level decline in incidence suggests reduced trigger exposure is effectively preventive (PMID: 33742666; PMID: 38902530).
- **Secondary prevention:** Detection via incidental ALP elevation or radiographs; no formal population screening program.
- **Tertiary prevention:** Bisphosphonates and vitamin D/calcium repletion to control active disease; orthopedic surveillance; prompt imaging + biopsy for suspected sarcoma.
- **Genetic counseling:** Appropriate for early-onset/familial (SQSTM1) disease and for autosomal-recessive JPD families; incomplete penetrance limits predictive value in classic PDB.
- **Immunization / prophylaxis:** Not applicable.

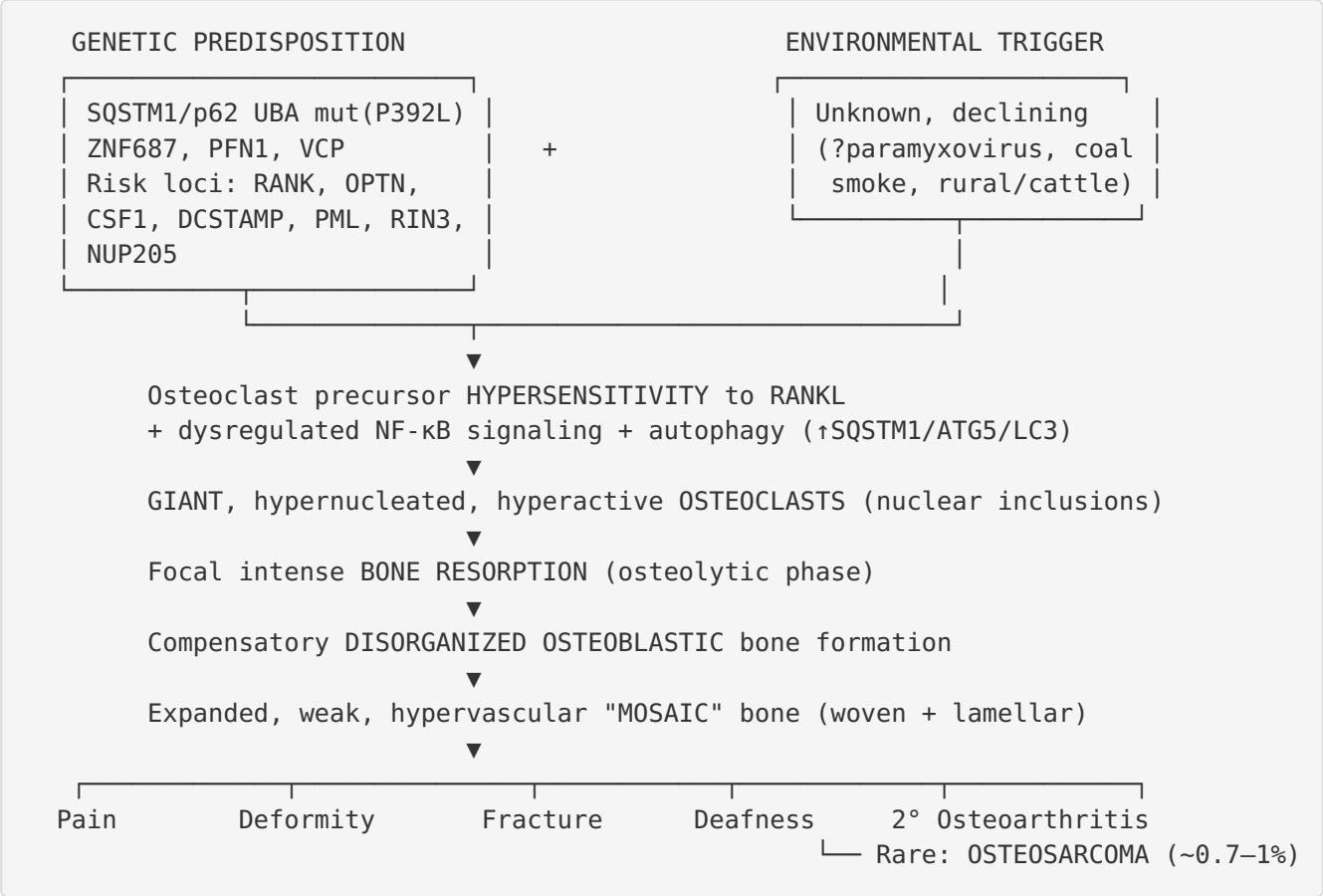
Section 14 — Other Species / Natural Disease

- **Taxonomy:** Human disease (*Homo sapiens*, NCBI:txid9606). Engineered mouse models exist (*Mus musculus*, NCBI:txid10090).
- **Orthologous genes:** mouse *Sqstm1*, *Vcp*, *Tnfrsf11b* (Opg), *Tnfrsf11a* (Rank), *Csf1*, *Optn*.
- **Natural disease in other species:** No well-established spontaneous PDB analog in companion animals in the reviewed literature; the epidemiologic association with cattle density (PMID: 40408225) is ecological, not evidence of a natural animal disease. Prior pet ownership (dogs/cats) was exonerated as a risk factor (PMID: 2376461).
- **Comparative biology:** The RANK–RANKL–OPG axis and p62/autophagy machinery are evolutionarily conserved, underpinning the translational validity of mouse models.
- **Zoonotic potential:** None demonstrated; the paramyxovirus/zoonosis hypotheses remain unproven (Section 5).

Section 15 — Model Organisms

- **P394L SQSTM1 knock-in mouse** (mammalian; equivalent to human p.P392L) — the key model. Heterozygotes develop focal pagetic-like lesions in 77% and homozygotes in 95% by 12 months vs 0% in wild-type (P<0.001), with enlarged multinucleated osteoclasts containing nuclear inclusions and increased RANKL sensitivity: "mice with a proline to leucine mutation at codon 394 of mouse sqstm1 (P394L) … develop a bone disorder with remarkable similarity to PDB" (PMID: 21515589). This model also demonstrated that zoledronic acid prevents pagetic-like lesions and accelerated bone loss (PMID: 30154079).
- **Phenotype recapitulation:** Excellent for the focal osteolytic/mixed lesions, giant osteoclasts, RANKL hypersensitivity, and autophagy dysregulation.
- **Limitations:** Requires the germline mutation plus aging; incomplete recapitulation of the human environmental trigger and of extensive polyostotic deforming disease; does not model osteosarcoma.
- **In-vitro systems:** Patient-derived and mutant osteoclast precursor cultures show increased RANKL sensitivity, giant osteoclast formation, and elevated SQSTM1/ATG5/LC3 (PMID: 21515589).
- **Resources:** MGI (mouse), Alliance of Genome Resources.

Mechanistic Model / Interpretation



Upstream vs downstream: SQSTM1/p62 dysfunction and RANK–RANKL–OPG imbalance are the most upstream molecular events; the osteoclast is the central effector; osteoblastic overactivity and mosaic bone are downstream consequences. Juvenile Paget's disease (OPG loss → unopposed RANKL) is a "natural experiment" that isolates the RANK–RANKL–OPG limb and confirms its centrality (Finding F008).

Evidence Base

PMID	How it supports / challenges findings
21515589	P394L knock-in mouse recapitulates PDB; establishes causal role of UBA mutation and autophagy dysregulation (F001, F009)
37180975	SQSTM1 as most frequent genetic cause; UBA mutations linked to severity (F001)
33742666	Declining UK incidence → changing environmental trigger (F002)
40408225	Rural livestock (cattle) association; environmental contribution (F002)
21638319	Durable remission from single zoledronic acid infusion (F003)
28176386	PRISM-EZ: intensive therapy gives no QoL/pain/fracture benefit (F003)
17550323	Paget sarcoma histology (88% osteosarcoma) and 10% 5-yr survival (F004)
1451058	0.7% malignant transformation incidence (F004)
40037468	VCP-MSP/IBMPFD — syndromic PDB (F005)
33145792	Shared stress-granule/autophagy defect across MSP genes (F005)
21623375	Seven GWAS loci; ~13% familial risk (F006)
31574000	Diagnostic workup + zoledronic acid first-line (F007)
32803929	Radiography + ALP + bone scan algorithm (F007)
32298837	OPG (TNFRSF11B) loss causes JPD; SP7 mutation (F008)
25108083	OPG genotype–phenotype correlation in JPD (F008)
33768371	Osteoclast as central effector cell (F009)
3701300 / 1805546 / 28361207 / 2376461	Conflicting/negative evidence on the paramyxovirus hypothesis

Limitations and Knowledge Gaps

1. **The environmental trigger is unidentified.** Declining incidence strongly implies one, but coal-smoke, paramyxovirus, and cattle-exposure hypotheses are unconfirmed and partly contradicted.
2. **Genotype–phenotype gaps.** SQSTM1 and the seven GWAS loci explain only a minority of heritability; many familial cases are unexplained (PMID: 41024681).
3. **Epigenetics.** No robust disease-specific DNA-methylation/histone dataset was identified.
4. **Treatment paradox.** Excellent biochemical control does not translate into fewer fractures or better QoL (PRISM-EZ), leaving the optimal treatment goal (biochemical vs symptomatic) unresolved.
5. **Sarcoma risk stratification.** No reliable biomarker predicts which patients will undergo malignant transformation; surveillance guidelines are underdeveloped (PMID: 42359209).
6. **Modern data are cohort/registry-based**, subject to referral and ascertainment bias; SEER-type survival data for classic PDB are limited.

Proposed Follow-up Experiments / Actions

1. **Trigger identification:** Metagenomic/16S and viral-capture sequencing of active pagetic bone vs controls, paired with geospatial exposure analysis (cattle density, historical coal use) to test environmental hypotheses definitively.
2. **Heritability completion:** Large multi-ancestry GWAS + WGS/burden testing in SQSTM1-negative families to find the missing causal genes.
3. **Epigenomic profiling:** ATAC-seq/WGBS/ChIP-seq of pagetic vs normal osteoclasts to map disease-specific regulatory changes.
4. **Randomized trial of a symptom-guided vs biochemical-target treatment strategy** with fracture, deformity progression, deafness, and validated QoL endpoints (extending PRISM-EZ).
5. **Sarcoma biomarker discovery:** Longitudinal imaging + circulating tumor DNA/somatic mutation surveillance in high-burden pagetic bone to enable early detection.
6. **Mechanistic dissection in models:** Cross P394L-Sqstm1 mice onto RANK/OPG-modified backgrounds and test autophagy modulators to define the causal hierarchy and identify targeted (non-bisphosphonate) therapies.

Report compiled from 9 confirmed findings and 39 primary papers over 5 investigation iterations. Evidence source types are indicated throughout: human clinical/registry, model organism (P394L mouse), in-vitro osteoclast, and computational/GWAS.