

SQSTM1-related Multisystem Proteinopathy (MSP3): A Comprehensive Disease Characterization

MONDO ID: MONDO:0800464 · **OMIM:** 616887 (MSP3) · **Gene:** *SQSTM1*/p62 (HGNC:11280; NCBI Gene 8878; UniProt Q13501; chr5q35) · **Category:** Mendelian **Report type:** Disease knowledge-base characterization · **Evidence base:** 10 confirmed findings, 60 papers reviewed

Summary

SQSTM1-related multisystem proteinopathy (MSP3) is a dominantly inherited, adult-onset, pleiotropic disorder caused by germline variants in *SQSTM1*, the gene encoding the autophagy receptor/signaling scaffold **p62/sequestosome-1**. A single genetic lesion produces a remarkably variable clinical spectrum: **inclusion body/distal myopathy (IBM/MRV)**, **amyotrophic lateral sclerosis (ALS)**, **frontotemporal dementia (FTD)**, and **Paget disease of bone (PDB)**, unified pathologically by p62- and TDP-43-positive protein aggregates and rimmed vacuoles. Most pathogenic variants cluster in the **ubiquitin-associated (UBA) domain**, with **p.P392L (c.1175C>T)** the single most common allele across populations ([PMID: 17229007](#)).

Mechanistically, the disease **branches from one p62 lesion into two arms**. A **gain-of-function bone arm** operates through enhanced RANK→NF-κB signaling that drives osteoclast overactivity and pagetic bone remodeling — but this arm is **incompletely penetrant and requires an environmental "second hit"** (paramyxoviral measles nucleocapsid protein acting via IL-6), as demonstrated in knock-in mice ([PMID: 24339057](#)). A **loss-of-function neuromuscular arm** reflects impaired selective autophagy and mitophagy, causing TDP-43 aggregation and degeneration of muscle and motor/cortical neurons. Strikingly, **biallelic loss-of-function** of the *same* gene produces a completely distinct **recessive childhood-onset neurodegeneration** with ataxia, dystonia, and vertical gaze palsy (DNECAS) ([PMID: 27545679](#)).

The clinical and prognostic bottom line is **organ-dependent**: the bone arm is largely **benign and highly treatable/preventable** with zoledronic acid — including genotype-guided prophylaxis that prevented new lesions in a randomized trial of *SQSTM1* carriers (PMID: 38123339) — whereas the neuromuscular arms (ALS/FTD, distal myopathy, childhood neurodegeneration) are **progressive, life-limiting, and lack disease-modifying therapy**. A rare but grave complication of the bone arm is malignant (osteosarcoma/giant-cell) transformation in <1% of polyostotic PDB, often associated with a *ZNF687* second-hit genotype (PMID: 32106343).

Key Findings

Finding 1 — *SQSTM1* causes a pleiotropic multisystem proteinopathy spanning IBM, ALS, FTD, and Paget disease of bone

Heterozygous *SQSTM1* variants produce a clinical spectrum encompassing **inclusion body myopathy (IBM), motor neuron disease/ALS, frontotemporal dementia (FTD), and Paget disease of bone (PDB)**, unified by shared **TDP-43- and p62-positive aggregate pathology and rimmed vacuoles**. *SQSTM1* is formally designated **MSP3 (OMIM 616887)**, one of a family of MSP genes that also includes *VCP*, *HNRNPA2B1*, and *HNRNPA1*.

As the landmark MSP review states: *"Mutations in VCP, HNRNPA2B1, HNRNPA1, and SQSTM1, encoding RNA-binding proteins or proteins in quality-control pathways, cause multisystem proteinopathies (MSP). They share pathological findings of protein aggregation and clinical combinations of inclusion body myopathy (IBM), neurodegeneration [motor neuron disorder (MND)/frontotemporal dementia (FTD)], and Paget disease of bone (PDB)"* (PMID: 36861178). In the Mayo Clinic MSP cohort, *SQSTM1*+*TIA1* accounted for 5 of 31 MSP individuals.

Demographically, a Chinese MSP cohort of 953 ALS/IBM/dementia patients identified 29 carriers of MSP-gene variants, with onset predominantly in the 3rd–5th decade and strong male predominance: *"Most patients were male (72.4%), with disease onset predominantly in the third to fifth decades of life. The majority of patients (21/29) presented with a single clinical phenotype"* (PMID: 41737544). The fact that **most patients present with a single phenotype** is central to the disease's clinical reality — full multisystem co-occurrence in one individual is the exception, not the rule.

Ontology anchors: MONDO:0800464 (disease); HP:0003198 (Myopathy); HP:0007354 (Amyotrophic lateral sclerosis); HP:0002145 (Frontotemporal dementia); HP:0002661 (Paget disease of bone).

Finding 2 — Pathogenic SQSTM1 variants cluster in the UBA domain and impair selective autophagy with NF-κB activation

In familial PDB, **all 14 initially reported SQSTM1 mutations affect the ubiquitin-associated (UBA) domain**, with **P392L** the most prevalent, present in both familial and sporadic cases across populations: *"The 14 mutations reported in SQSTM1/p62 all affect the ubiquitin-associated domain of the protein. The P392L mutation is the most commonly observed mutation in PDB patients"* (PMID: 17229007).

Functionally, the p62 protein is a multidomain scaffold: it binds ubiquitinated cargo via the UBA domain, LC3 via its LIR motif (acting as a selective autophagy receptor), and sequesters KEAP1 to activate the NFE2L2/Nrf2 antioxidant response. Pathogenic variants disrupt this machinery. Studies of the **p.R321C** variant demonstrate the dual mechanism: *"In vitro studies associated the p62-321C variant with a blockade of autophagy and with the activation of the NF-κB pathway"* (PMID: 40374720). A humanized p62-321C mouse developed stimulus-induced seizures, CNS p62/cFos changes, and degenerating spinal motor neurons.

Ontology anchors: GO:0005515 (protein binding); GO:0061136 (regulation of proteasomal protein catabolic process); GO:0000421 (autophagosome membrane); GO:0038061 (NIK/NF-κB signaling). Protein: UniProt Q13501, UBA domain residues ~389–434.

Finding 3 — Biallelic SQSTM1 loss-of-function causes a distinct recessive childhood-onset neurodegeneration (DNECAS)

In sharp mechanistic contrast to the dominant adult disease, **biallelic (recessive) loss of p62** produces a childhood/adolescence-onset neurodegenerative disorder. Haack et al. *"identified three different biallelic loss-of-function variants in SQSTM1 in nine affected individuals from four families with a childhood- or adolescence-onset neurodegenerative disorder characterized by gait abnormalities, ataxia, dysarthria, dystonia, vertical gaze palsy, and cognitive decline"* (PMID: 27545679).

Affected fibroblasts showed **complete absence of p62 protein** and investigators "*found evidence of a defect in the early response to mitochondrial depolarization and autophagosome formation*" (PMID: 27545679) — directly implicating a **mitophagy/autophagy-initiation defect**. A novel homozygous frameshift (c.790del) was subsequently reported in childhood-onset progressive neurodegeneration with ataxia and gaze palsy (PMID: 35957775).

Ontology anchors: HP:0001251 (Ataxia); HP:0001332 (Dystonia); HP:0031605 (Vertical gaze palsy); HP:0100543 (Cognitive impairment); GO:0000423 (mitophagy).

Finding 4 — Epidemiology: SQSTM1 is the most common PDB gene; PDB prevalence ~1–2% in older adults but declining, male-predominant, with strong geographic variation

Paget disease of bone, the most frequent *SQSTM1*-associated phenotype, affects **~1–2% of adults over 55** in high-prevalence regions (UK, Western Europe), with marked geographic clustering (highest in NW England) and a **continuing secular decline**. In the UK, "*the overall standardized incidence decreased from 0.75/10,000 person-years in 1999 to 0.20/10,000 person-years in 2015*" (PMID: 33742666).

Prevalence is far lower in Asian populations. In South Korea, researchers reported "*a mean prevalence of 1.20 per 100,000 and an age-adjusted incidence ranging from 0.38 to 1.26 per 100,000 person-years*" (PMID: 39906256). PDB is **male-predominant and strongly age-dependent**, with crude incidence rising from ~0.04–0.07/10,000/yr at age 45–49 to 3.7–6.3/10,000/yr at ≥85.

The **full SQSTM1-MSP syndrome** (neuromuscular + bone) is much rarer than isolated PDB: MSP overall was found in only 3.0% (29/953) of a Chinese ALS/IBM/dementia cohort, and a Japanese nationwide survey ascertained only 47 MSP patients (PMID: 38287512). The secular decline and a **rural/livestock (cattle density)** association point to an environmental contribution: "*A moderately positive correlation ($R^2 = 0.236$) was identified between PDB incidence and the density of female breeding cattle*" (PMID: 40408225).

Population / Region	Metric	Value	Source
UK (1999)	Standardized incidence	0.75 / 10,000 PY	PMID: 33742666
UK (2015)	Standardized incidence	0.20 / 10,000 PY	PMID: 33742666
South Korea	Mean prevalence	1.20 / 100,000	PMID: 39906256
South Korea	Age-adjusted incidence	0.38–1.26 / 100,000 PY	PMID: 39906256
China (MSP cohort)	MSP among ALS/IBM/dementia	29/953 (3.0%)	PMID: 41737544
Japan	Nationwide MSP patients	47	PMID: 38287512

Finding 5 — Treatment: Zoledronic acid durably controls SQSTM1-associated PDB, and genetic-test-guided prophylaxis can prevent bone lesions

Intravenous **zoledronic acid** (an aminobisphosphonate; NCIT:C1699) is the mainstay for the bone component. In a long-term retrospective cohort, biochemical response favored treatment strongly: *"Primary outcome was more prevalent in the ZOL compared to the NZOL group [42 patients (88%) VS 11 patients (52%) respectively, $P = 0.004$]"* ([PMID: 38555314](#)), with sustained normalization of alkaline phosphatase.

Most importantly, the **ZiPP/PREVENT-PDB randomized trial** of 222 *SQSTM1*-pathogenic-variant carriers showed that **prophylactic zoledronic acid prevented new bone lesions**: *"Eight of the placebo group had a poor outcome (lesions which were new, unchanged or progressing) compared with none of the ZA group (OR 0.08, 95% CI 0.00 to 0.42, $p=0.003$)"* over a median 84 months ([PMID: 38123339](#)). This is a rare example of **genotype-guided precision prevention** in a Mendelian disease.

The acute phase response (fever, myalgia) after zoledronate can be attenuated by a short course of dexamethasone ([PMID: 36970850](#)). By contrast, **no disease-modifying therapy exists** for the myopathy/ALS/FTD components, which are managed supportively (physiotherapy, occupational therapy, respiratory care).

Ontology anchors: NCIT:C1699 (Zoledronic Acid); NCIT:C1455 (Bisphosphonate); NCIT:C575 (Dexamethasone); CHEBI:46557 (zoledronic acid).

Finding 6 — TIA1/SQSTM1 digenic late-onset distal myopathy defines a homogeneous SQSTM1 muscle phenotype, with SQSTM1 acting as a modifier

The muscle arm of *SQSTM1* disease is frequently **digenic**. Co-inheritance of **TIA1 p.Asn357Ser** and **SQSTM1 p.Pro392Leu** produces a strikingly homogeneous phenotype: *"These twenty-four patients (75% males) had late-onset ($52,6 \pm 10,1$ years), mainly asymmetric, distal ankle and hand finger extension weakness (75%), mild CK elevation (82.4%) and myopathic EMG"* (PMID: 39142003).

The TIA1 allele is enriched in distal myopathy panels and is proposed as a genetic modifier: *"We confirm an increased burden of the TIA1 p.Asn357Ser variant in distal myopathy patients which could act as a genetic modifier"* (PMID: 39142003). An independent Spanish report confirmed that *"a similar phenotype has been attributed to the digenic inheritance of TIA1 c.1070A>G (p.Asn357Ser) and SQSTM1 c.1175C>T (p.Pro392Leu) variants"* (PMID: 38016875). Muscle biopsy shows rimmed vacuoles (combined 44–83%) with p62/TDP-43 aggregates. Notably, *SQSTM1* can also cause **proximal** myopathy with rimmed vacuoles via a frameshift variant, broadening the muscle phenotype (PMID: 36998782).

Ontology anchors: HP:0003693 (Distal amyotrophy); HP:0003805 (Rimmed vacuoles); HP:0003236 (Elevated circulating creatine kinase); HP:0003458 (EMG: myopathic abnormalities); HP:0030319 (Finger extensor weakness).

Finding 7 — Mutant p62 potentiates RANK-induced NF-κB activation and osteoclastogenesis (bone arm) and accelerates ALS progression (neuro arm)

On the **bone side**, PDB-associated p62 mutants act by **gain-of-function on NF-κB**: *"p62 mutants increased NF-kappaB activation and significantly potentiated osteoclast formation and bone resorption in human primary cell cultures"* (PMID: 16813535). This study described a novel **K378X** truncation causing a severe polyostotic phenotype alongside P392L and E396X.

On the **neurodegeneration side**, *SQSTM1* missense variants span the PB1, TRAF6-binding, PEST, and UBA domains and **worsen prognosis**. In a Chinese ALS cohort, *"the ΔFS analysis revealed that the risk of death or tracheostomy was significantly increased in SQSTM1 mutation carriers ($p < 0.05$)"* (PMID: 25708934). Neuropathologically, p62 immunohistochemistry reliably labels TDP-43-positive and C9RANT-positive neuronal cytoplasmic inclusions in FTL/ALS tissue.

Ontology anchors: GO:0038061 (NIK/NF-κB signaling); GO:0045670 (regulation of osteoclast differentiation); CL:0000092 (osteoclast); CL:0000100 (motor neuron).

Finding 8 — Diagnostic workup is organ-specific

Diagnosis depends on which arm is manifest:

- **Bone arm (PDB):** Usually detected incidentally via isolated **elevated serum total/bone alkaline phosphatase** (elevated in ~90% of PDB; LOINC 6768-6) or on radiographs. *"Most cases of PDB are diagnosed incidentally on radiographs or as an isolated elevation of serum alkaline phosphatase... Diagnosis is made on the basis of typical radiological features on plain films, while a radionuclide bone scan may be used to assess the extent of disease"* (PMID: [33543158](#)). Pathognomonic radiographic features include cortical thickening, medullary expansion, osteolytic "blade of grass" fronts, and mixed lytic-sclerotic skull; histology shows mosaic cement lines. Bone-turnover markers (CTX, P1NP) are elevated.
- **Neuromuscular arm:** Requires **needle EMG** (myopathic ± neurogenic), **muscle MRI** (distal fatty replacement, e.g., medial gastrocnemius), and **muscle biopsy**: *"Muscle biopsy showed rimmed vacuoles (44.4%), myofibrillar disorganization (16.7%) or both (38.9%), with P62/TDP43 aggregates"* (PMID: [39142003](#)).
- **Definitive diagnosis is molecular:** Targeted *SQSTM1* sequencing or multigene MSP/ALS/distal-myopathy NGS panels (including *TIA1*), with WES/WGS for atypical cases.

Ontology anchors: LOINC 6768-6 (Alkaline phosphatase); NCIT:C17007 (genetic testing); HP:0003236 (elevated CK).

Finding 9 — Mouse models show p62 P394L (= human P392L) causes osteoclast RANKL-hyperresponsiveness but requires a second hit for full Paget lesions

The gene-environment nature of the bone arm is directly demonstrated in mice. *"We generated p62(P394L) knock-in mice (p62KI) and found that although OCL numbers were increased, the mice did not develop pagetic lesions. However, mice expressing both MVNP and p62KI developed more exuberant pagetic lesions than mice expressing MVNP alone"* (PMID: [24339057](#)). The downstream mediator is IL-6: *"Interleukin-6 (IL-6) production is essential for the pagetic phenotype, because transgenic mice with MVNP targeted to OCLs develop pagetic OCLs and lesions, but this phenotype is absent when MVNP mice are bred to IL-6(-/-) mice"* (PMID: [24339057](#)).

This explains **incomplete, age-dependent penetrance** of PDB: the p62 UBA mutation primes osteoclasts to RANKL but, alone, is insufficient; a paramyxoviral/inflammatory "second hit" acting through IL-6 is needed for full lesions. Available model systems therefore include:

p62(P394L) knock-in mice (bone), the **humanized p62-R321C mouse** (CNS: seizures, motor-neuron degeneration; [PMID: 40374720](#)), **Sqstm1/p62-null mice** (mitophagy defect; models the biallelic human phenotype), and **patient fibroblasts/iPSC** and **RAW264.7 osteoclast cultures**.

Ontology anchors: NCBI Taxon 10090 (*Mus musculus*); MGI *Sqstm1*; CL:0000092 (osteoclast); GO:0032635 (interleukin-6 production).

Finding 10 — Prognosis is organ-specific: PDB arm usually benign/treatable but <1% undergo osteosarcoma transformation; neuro arm is progressive and life-limiting

Most *SQSTM1*-associated PDB is **mild and monostotic** (77% monostotic; only 3% fracture in one cohort) and controllable with bisphosphonates. Complications include bone pain, deformity, fractures, deafness (skull involvement), compression neuropathy/spinal cord compromise, secondary osteoarthritis, and high-output cardiac states.

The gravest bone complication is **malignant transformation**: *"Neoplastic transformation is a rare but serious complication of Paget's disease of bone (PDB), occurring in fewer than 1% of individuals with polyostotic disease. Their prognosis is poor, with less than 50% surviving 5 years"* ([PMID: 32106343](#)). Spinal pagetic osteosarcoma has a 5-year survival as low as 10% ([PMID: 42359209](#)). Transformation is associated with a **germline ZNF687 P937R founder mutation** and **dual SQSTM1+ZNF687 genotypes** — a case report documented *"genetic testing confirming dual SQSTM1 and ZNF687 mutations"* ([PMID: 41630218](#)).

In contrast, the **neuromuscular components are relentlessly progressive**: distal myopathy causes slowly progressive disability over 10+ years; *SQSTM1*-ALS carriers have accelerated decline and shortened survival ([PMID: 25708934](#)); FTD and the biallelic childhood neurodegeneration are progressive and fatal.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

Shared initiating lesion: 1. A germline *SQSTM1* variant (most commonly a **UBA-domain missense, e.g., p.P392L**) **alters p62 function** → impairs ubiquitin-cargo binding and p62's dual role as autophagy receptor and signaling scaffold ([PMID: 17229007](#)).

The pathway then **branches** according to cell type, gene dose (mono- vs biallelic), and environment:

BRANCH A — Bone (gain-of-function, environment-gated): 2A. Mutant p62 **potentiates RANK→NF-κB signaling** in osteoclast precursors (PMID: 16813535) → **leads to** osteoclast RANKL-hyperresponsiveness and increased osteoclast number. 3A. Alone this is **insufficient** (p62KI mice do not develop lesions) → a **second hit** (paramyxoviral MVNP; inferred from epidemiologic measles/livestock associations) **acts via IL-6** (PMID: 24339057) → **results in** exuberant, disorganized bone remodeling. 4A. **Leads to** focal accelerated bone turnover → cortical thickening, medullary expansion, deformity, fractures, deafness → clinical **Paget disease of bone**. 5A. Rarely (<1%, often with a ZNF687 second hit) → **malignant transformation to osteosarcoma** (PMID: 32106343).

BRANCH B — Neuromuscular (loss-of-function / impaired autophagy): 2B. Mutant p62 **blocks selective autophagy and impairs mitophagy** (PMID: 40374720) → **leads to** accumulation of ubiquitinated cargo and damaged mitochondria. 3B. **Results in** cytoplasmic TDP-43 and p62 aggregation with rimmed vacuoles in myofibers and neurons (PMID: 39142003). 4B. Co-modifier alleles (e.g., TIA1 p.N357Ser) lower the threshold → **digenic distal myopathy** (PMID: 39142003); in motor/cortical neurons → **ALS/FTD** with accelerated progression (PMID: 25708934).

BRANCH C — Recessive childhood neurodegeneration (complete loss-of-function): 2C. Biallelic LoF → **complete absence of p62 protein** → defective early mitophagy response (PMID: 27545679) → **leads to** childhood-onset neurodegeneration with ataxia, dystonia, gaze palsy (DNECAS).

Branch comparison table

Feature	Bone arm (PDB)	Neuromuscular arm (IBM/ ALS/FTD)	Recessive childhood (DNECAS)
Inheritance	Autosomal dominant	Autosomal dominant ($\pm$ digenic)	Autosomal recessive
Dominant mechanism	Gain-of-function (NF- κ B $\uparrow$)	Loss-of-function (autophagy $\downarrow$)	Complete LoF (no p62)
Variant type	UBA missense (P392L)	Missense across domains; truncating	Biallelic truncating/ frameshift
Second hit needed	Yes (MVNP/IL-6)	Modifier alleles (TIA1)	No
Onset	Older adult (>55)	3rd–5th decade	Childhood/ adolescence
Penetrance	Incomplete, age- dependent	Incomplete, variable	High (recessive)
Pathology	Mosaic cement lines, osteoclast $\uparrow$	p62/TDP-43 aggregates, rimmed vacuoles	Mitophagy defect
Prognosis	Benign, treatable	Progressive, life-limiting	Progressive, fatal
Therapy	Zoledronic acid (preventable!)	Supportive only	Supportive only

Evidence Base

PMID	Title (abbreviated)	Supports finding(s)	Evidence type
36861178	MSPs and MSP-like disorders: spectrum	F1 (disease definition)	Human clinical / review
41737544	Chinese MSP genetic spectrum	F1, F4 (demographics)	Human clinical cohort
17229007	SQSTM1 mutation frequencies/haplotypes	F2 (UBA clustering, P392L)	Human genetics
40374720	p.R321C CNS abnormalities	F2 (autophagy/NF- κ B), F9 (mouse)	In vitro + mouse
27545679	Biallelic SQSTM1 childhood neurodegeneration	F3 (DNECAS)	Human genetics + fibroblasts
35957775	Novel c.790del recessive case	F3	Human case
33742666	UK PDB declining incidence	F4 (epidemiology)	Epidemiology
39906256	South Korea PDB epidemiology	F4	Epidemiology
40408225	PDB decline & livestock association	F4 (environment)	Epidemiology
38287512	Japan nationwide MSP survey	F4	Epidemiology
38555314	Zoledronic acid long-term effectiveness	F5 (treatment)	Clinical cohort
38123339	ZiPP/PREVENT-PDB RCT (genotype-guided)	F5 (prevention)	Randomized trial
36970850	Dexamethasone for zoledronate APR	F5 (adverse-event mgmt)	Randomized trial
39142003	TIA1/SQSTM1 digenic myopathy landscape	F6, F8 (diagnosis)	Human clinical cohort
38016875	Digenic TIA1/SQSTM1 Spanish patients	F6	Human case series
36998782	Frameshift SQSTM1 proximal MRV	F6	Human case

PMID	Title (abbreviated)	Supports finding(s)	Evidence type
16813535	K378X, NF-κB, osteoclastogenesis	F7 (bone mechanism)	In vitro functional
25708934	Six SQSTM1 mutations in Chinese ALS	F7, F10 (prognosis)	Human genetics
33543158	Paget's disease clinical update	F8 (diagnosis)	Clinical review
24339057	IL-6/MVNP + p62 P394L knock-in mice	F9 (GxE, model)	Mouse model
32106343	ZNF687 in neoplastic PDB transformation	F10 (prognosis)	Human genetics
41630218	Spinal PDB malignant transformation	F10	Human case
42359209	Pagetic spinal osteosarcoma review	F10	Clinical review

Challenges / nuances: The VCP-focused MSP therapeutic literature (rapamycin/chloroquine, exercise training; e.g. [PMID: 24130765](#)) is encouraging for the autophagy-targeting concept but is **not SQSTM1-specific**, and one key paper was retracted ([PMID: 25884947](#)) — it should not be over-extrapolated to *SQSTM1*. The livestock/measles environmental link is **correlational** ($R^2=0.236$) and mechanistically supported only in mice, not proven in human *SQSTM1* carriers.

Section-by-Section Knowledge-Base Content

1. Disease Information. Adult-onset dominant multisystem proteinopathy (MSP3, OMIM 616887, MONDO:0800464) plus a distinct recessive pediatric neurodegeneration (DNECAS). Synonyms: *SQSTM1-related MSP*; p62-related myopathy/ALS/FTD/PDB. Information is aggregated from case series, cohorts, and registries (disease-level), not single-patient EHR.

2. Etiology. Primary cause: germline *SQSTM1* variants. Genetic risk: UBA-domain missense (P392L most common); modifier *TIA1* p.N357Ser (muscle), *ZNF687* P937R (malignant transformation). Environmental: paramyxovirus (measles/MVNP), rural/cattle exposure, age, male sex. Gene-environment interaction is proven in mice (p62KI requires MVNP/IL-6; [PMID: 24339057](#)).

3. Phenotypes. PDB (HP:0002661), distal amyotrophy (HP:0003693), rimmed vacuoles (HP:0003805), elevated CK (HP:0003236), ALS (HP:0007354), FTD (HP:0002145), ataxia (HP:0001251), dystonia (HP:0001332), gaze palsy (HP:0031605), hearing loss (HP:0000365), cognitive decline (HP:0100543). Onset mostly 3rd–5th decade (neuromuscular) or >55 (bone); childhood for recessive form. Progressive for neuro arm; treatable/stable for bone.

4. Genetic/Molecular. *SQSTM1* (HGNC:11280, chr5q35, UniProt Q13501). Variants: missense, nonsense (K378X, E396X), frameshift. Classification per ACMG; P392L pathogenic. Modifier genes: *TIA1*, *ZNF687*. Rare in gnomAD. Germline origin. Functional consequence: gain-of-function (NF- κ B/bone) and loss-of-function (autophagy/neuro).

5. Environmental. Paramyxovirus/measles nucleocapsid (via IL-6), livestock/rural exposure; secular decline implies modifiable environmental component.

6. Mechanism. See causal chain above. Pathways: RANK–NF- κ B (KEGG), selective autophagy/mitophagy (GO:0000423), KEAP1–NFE2L2. Cell types: osteoclast (CL:0000092), motor neuron (CL:0000100), skeletal myofiber.

7. Anatomy. Bone (UBERON:0001474; skull, spine, pelvis, long bones), skeletal muscle (UBERON:0001134; distal > proximal), spinal cord/motor neurons, frontotemporal cortex, cerebellum. Subcellular: autophagosome (GO:0005776), lysosome, mitochondrion.

8. Temporal. Adult/late onset (bone, >55; neuromuscular, 3rd–5th decade), childhood for recessive. Insidious, chronic, progressive (neuro) vs. focal/stable (bone).

9. Inheritance/Population. AD (dominant arms), AR (DNECAS), often digenic. Incomplete, age-dependent penetrance. Variable expressivity. PDB ~1–2% in high-prevalence regions, declining; male-predominant; NW England clustering.

10. Diagnostics. ALP + bone-turnover markers + radiography/bone scan (bone); EMG + muscle MRI + biopsy with p62/TDP-43 (muscle); molecular *SQSTM1* sequencing / NGS panels (definitive).

11. Prognosis. Bone arm benign/treatable, <1% osteosarcoma (poor, <50% 5-yr survival). Neuro arm progressive, life-limiting; ALS carriers have shortened survival.

12. Treatment. Zoledronic acid (NCIT:C1699) for PDB — including genotype-guided prophylaxis; dexamethasone for APR; supportive care (PT/OT, respiratory) for neuromuscular arms. No disease-modifying neuro therapy.

13. Prevention. Primary/secondary: genetic testing + prophylactic zoledronic acid in *SQSTM1* carriers (proven in ZiPP RCT); genetic counseling; cascade testing. Tertiary: bisphosphonates to prevent deformity/complications.

14. Other species. Mouse (NCBI Taxon 10090) ortholog *Sqstm1*; p62(P394L) knock-in and p62-null models. No major naturally occurring animal disease documented.

15. Model organisms. p62(P394L) knock-in (bone), humanized p62-R321C (CNS), *Sqstm1*-null (mitophagy/recessive), patient fibroblasts/iPSC, RAW264.7 osteoclast cultures.

Limitations and Knowledge Gaps

1. **No dedicated SQSTM1-MSP primary dataset was analyzed** — this report synthesizes published literature; all statistics are extracted from cited studies.
 2. **Penetrance and genotype-phenotype rules are imprecise.** Why one carrier develops PDB, another ALS, and another nothing is unexplained beyond modifier alleles and environmental hits.
 3. **The environmental "second hit" is proven only in mice.** The measles/MVNP-IL-6 axis and livestock correlation ($R^2=0.236$) are not mechanistically confirmed in human *SQSTM1* carriers.
 4. **No disease-modifying therapy for the neuromuscular arms.** Autophagy-modulating strategies remain extrapolations from *VCP* models (one key paper retracted).
 5. **Cohorts are small and geographically skewed** (Europe, East Asia); carrier frequency, incidence of the full MSP syndrome, and sex ratios for the neuromuscular arms are poorly quantified.
 6. **Prognostic biomarkers are lacking** for predicting which carriers will convert to neurodegeneration.
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Proposed Follow-up Experiments / Actions

1. **Genotype-phenotype registry:** Pool international *SQSTM1* carriers to estimate arm-specific penetrance, modifier burden (*TIA1*, *ZNF687*), and environmental covariates.
2. **Test the viral second-hit hypothesis in humans:** Serological/PCR studies for paramyxovirus exposure stratified by *SQSTM1* genotype and PDB status.
3. **iPSC-derived osteoclast + motor-neuron isogenic panels** carrying P392L, R321C, and biallelic LoF to dissect the gain- vs loss-of-function branch point quantitatively.

4. **Biomarker discovery:** Longitudinal serum/CSF neurofilament, TDP-43, and bone-turnover markers to predict neuromuscular conversion in asymptomatic carriers.
 5. **Therapeutic trials of autophagy enhancers** specifically in *SQSTM1* muscle/neuron models before clinical translation.
 6. **Extend prophylaxis evidence:** Longer-term ZiPP follow-up and health-economic analysis to inform guidelines on genotype-guided zoledronic acid.
 7. **Screen for ZNF687 co-mutation** in polyostotic *SQSTM1*-PDB patients as a malignant-transformation risk stratifier.
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Report compiled from 10 confirmed findings across 5 investigation iterations and 60 reviewed papers. Evidence types span human clinical cohorts, human genetics, in vitro functional assays, mouse models, and epidemiology.

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