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The role of genetic diagnosis in the prevention of Paget's Disease of Bone Type 3 - A review of the literature

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ABSTRACT

Paget's disease of bone is a chronic condition that affects the typical structure and turnover of specific bones. Inherited forms, especially type 3, are commonly associated with mutations in the SQSTM1 gene. Although Paget's disease of bone has a genetic basis, it is usually diagnosed late, reducing treatment effectiveness. This review highlights why early genetic testing matters to prevent and manage Paget's disease of bone type 3, focusing on recent research, especially the Zoledronate in the Prevention of Paget's Disease trial. Traditionally, Paget's disease of bone is treated with bisphosphonates once symptoms appear. The earlier SQSTM1 mutations are found in symptom-free individuals, allowing for earlier treatment. The research found that preventive use of zoledronic acid in people with these mutations might slow down or even halt the disease. These results support adding genetic testing to routine care for those at risk and highlight the move toward being proactive in medicine, instead of just reacting to problems as they arise. The study shows that beginning treatment before symptoms develop - by catching genetic mutations early - could benefit patients.

Keywords: Paget's disease of bone, PDB3, SQSTM1, genetic diagnostics, Sanger sequencing.

1. INTRODUCTION

Paget's disease of the bone (PDB) is the second most frequently occurring metabolic bone disease in adults, after osteoporosis (Gennari et al., 2022). Its first description was made in 1877 by British surgeon James Paget, representing the progressive bone deformation and enlargement in aged patients (Banaganapalli et al., 2023). Although more than 140 years have passed since then, the etiology and molecular pathogenesis of this disease continue to be under intensive investigation. The main pathomechanism of PDB involves increased osteoclast activity and enhanced bone resorption. Osteoblast function is not sufficient to compensate for the osteoclast activity, which leads to the formation of deformed, thickened bones that are highly susceptible to fractures (Gennari et al., 2022; Ralston, 2020). The lesions are generally localized and are most frequently found in the skull, pelvis, femurs, and vertebrae (Ralston, 2020; Langston and Ralston, 2004). Disease is asymptomatic in

most cases, and it is usually found incidentally, for example, upon imaging or after measurement of increased alkaline phosphatase (ALP) activity (Gennari et al., 2019). Symptoms, if present, are usually bone pain, bone deformity, pathological fractures, and neurologic symptoms related to the pressure on nerve structures secondary to the osteoma formation (Gennari et al., 2019; Ralston, 2020). In severe forms, elaborative osteoarticular symptoms, secondary osteoarthritis, hearing loss (if the temporal bone is involved), and a hyperdynamic circulation leading to cardiomyopathy can be observed (Langston and Ralston, 2004; Michou and Brown, 2011). Most reports of PDB were received from the UK, Australia, New Zealand, France, and Italy (Banaganapalli et al., 2023; Cundy et al., 2004). Regions like Quebec and Lancashire have described clusters of people affected by the disease. That pattern suggests that both environmental and genetic factors can be involved. Things like industrial pollution, certain viral infections, or low vitamin D levels could all play a part (Michou and Brown, 2011; Whyte, 2006; Visconti et al., 2010).

Molecular Mechanisms and Pathogenesis

PDB can be sporadic or familial. About forty percent of patients with a positive family history occur as autosomal dominant with incomplete penetrance (PDB type 3) (Banaganapalli et al., 2023; Gennari et al., 2022).

The SQSTM1 gene mutation is characterized by strong relevance to the high risk of developing the familial form of PDB. Its product, p62, plays several vital roles in the cell. It takes part in autophagy, maintaining protein balance, managing oxidative stress, and regulating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription.

NF-κB is crucial for osteoclast formation (Gennari et al., 2019; Langston and Ralston, 2004). The p62 protein acts as an adaptor. It connects polyubiquitinated proteins to autophagosomes for their degradation under physiological conditions (Rea et al., 2009; Rea et al., 2013). It is also involved in signaling from other receptors, such as Receptor Activator of Nuclear Factor κB (RANK), which is essential for osteoclast differentiation (Gennari et al., 2004; Hocking et al., 2002). In addition to its role in NF-κB activity, p62 regulates oxidative stress. During oxidative stress, p62 binds to Kelch-like ECH-associated protein 1 (Keap1) and prevents Nrf2 breakdown. Increased Nrf2 levels stimulate the antioxidant gene expression (Duran et al., 2011). Mutations in SQSTM1 impair both the regulation of osteoclasts and cellular stress responses, contributing to abnormal bone remodeling, leading to an increased risk of fractures. To date, more than thirty pathogenic SQSTM1 mutations have been identified in cases of PDB. The majority of them are in exons seven and eight, which encode for the ubiquitin-associated domain of p62 (Rea et al., 2013; Duran et al., 2011). The most common is a missense mutation p.Pro392Leu (P392L) that impairs the p62 protein from binding polyubiquitinated protein. Missense mutations, such as P392L, decrease the stability of the ubiquitin-associated domain, while nonsense and frameshift mutations could result in complete loss of domain function or truncated, nonfunctional proteins (Chamoux et al., 2009; Whyte, 2006).

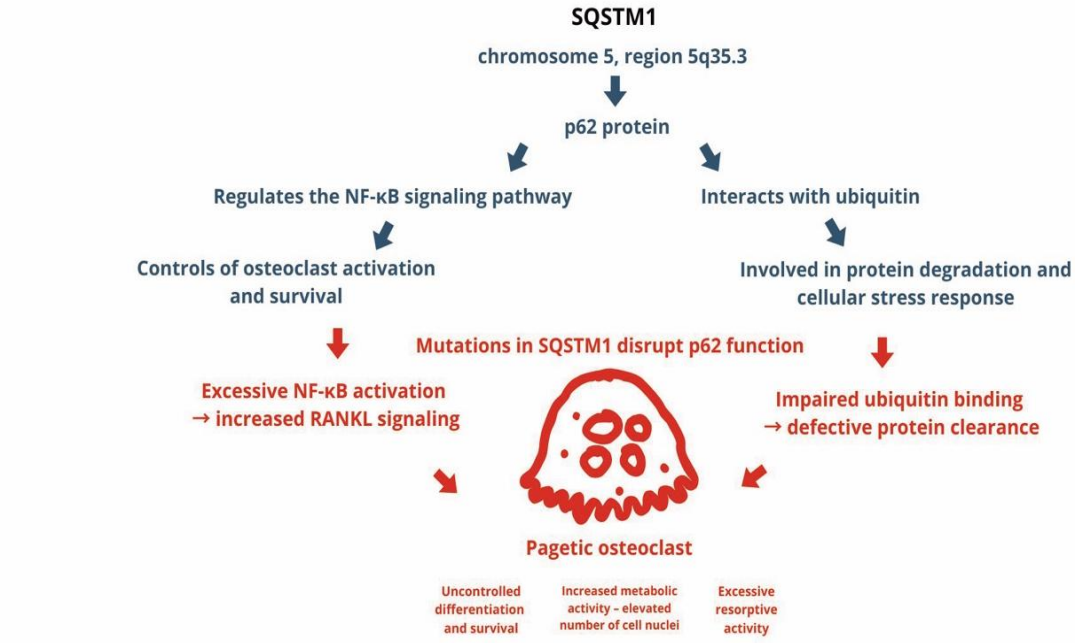

Figure 1: Mechanism of SQSTM1 mutation and dysregulation of osteoclast function in PDB3.

Consequently, p62 no longer properly controls osteoclast function, resulting in overactive bone resorption and, eventually, disorganized new bone formation – the PDB signature. Mutations in SQSTM1 carriers, especially the P392L variant, present an earlier onset of PDB, often occurring before the age of fifty. These individuals usually have a more severe, often polyostotic course of disease, and they are more likely to develop complications such as pathological fractures, deformities, and symptoms of neurological compression (Hocking et al., 2002; Duran et al., 2011).

The functional impact of SQSTM1 mutations has also been investigated in animal models. Of note, transgenic mice that specifically express the human P392L mutation in p62 also develop clinical features resembling PDB, including enhanced osteoclast number, high bone turnover, and focal lytic bone lesions (Chamoux et al., 2009).

These models are consistent with the idea that SQSTM1 mutations cause the disease and provide, for that reason, an effective system for the investigation of therapeutic options. Ultimately, PDB develops through interactions between genetic predisposition and cellular dysfunction. Dysregulation of the adaptor protein p62 encoded by the SQSTM1 gene, through a spectrum of mutation types, is a central molecular driver of the excessive and disorganized bone turnover observed in PDB3 (Rea et al., 2009; Rea et al., 2013; Gennari et al., 2004; Hocking et al., 2002; Duran et al., 2011; Chamoux et al., 2009; Phillips et al., 2024). Figure 1 shows the mechanism of SQSTSM1 mutation and dysregulation of osteoclast function in PDB3.

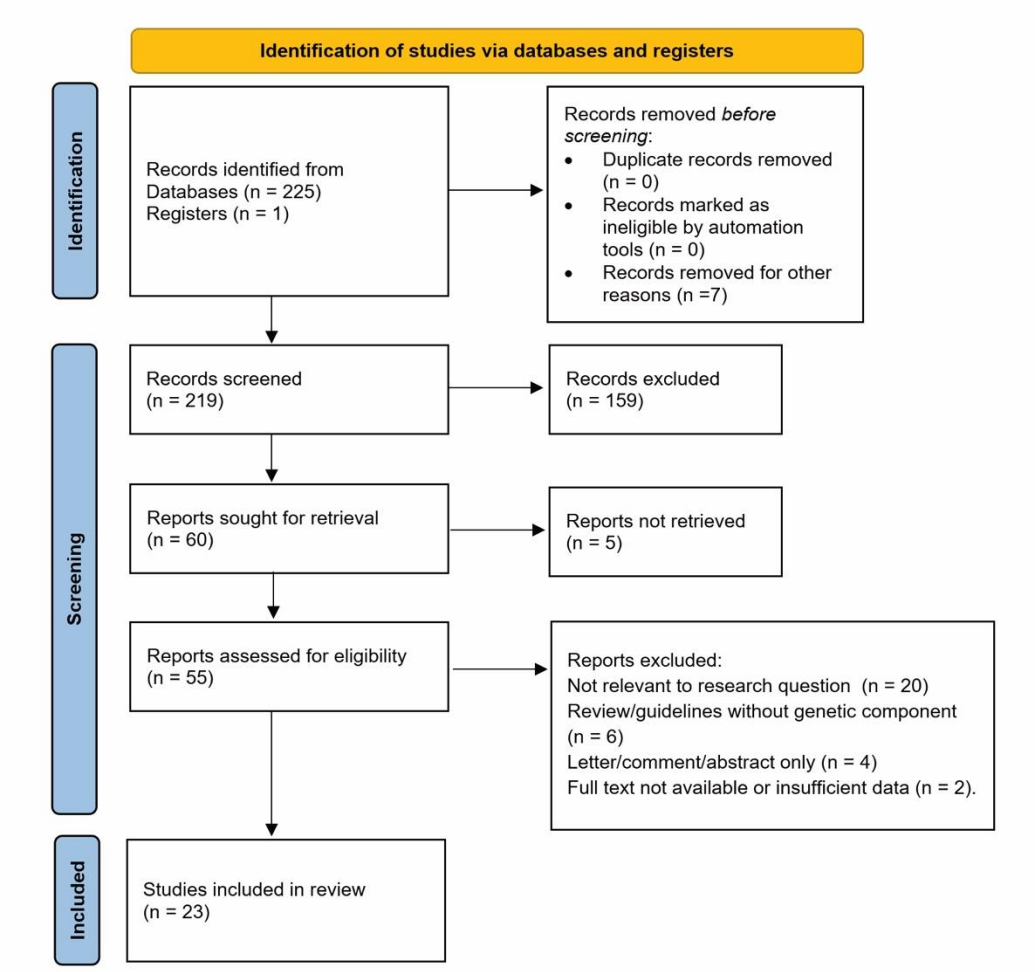

Figure 2: PRISMA flow diagram

2. REVIEW METHODS

A systematic literature review was conducted using the PubMed and Google Scholar databases. Original research articles, clinical trials, and reviews on the role of genetic tests in PDB type 3 served as the basis for the analysis. Informative abstracts provided us with relevant data when full-text articles were unavailable. We gave special attention to the Zoledronate in the Prevention of Paget's Disease

(ZiPP) trial, a major randomized controlled study. The review includes studies from 2002 to 2025. Keywords selected based on their relevance to examining the matter in the subject, such as: Paget's disease of bone, SQSTM1 mutation, PDB3, genetic screening, and clinical prevention. Each study was written exclusively in English. We applied the keywords in various combinations with logical operators.

The first step in the selection of the literature needed for review consisted of reviewing the titles and abstracts. The selected articles, then, were screened based on the full text by two independent researchers. Disagreements in evaluations were resolved through consensus to ensure the high quality and reliability of the selected sources.

Exclusion criteria:

- Articles not related to PDB disease or the role of genetic tests in PDB disease,
- Studies without an apparent reference to genetic diagnosis or treatment outcomes.

Twenty-three articles were finally selected based on the criteria mentioned earlier. The article screening process adhered to the PRISMA guidelines (Figure 2).

3. RESULTS

Several genes are known to cause PDB, including SQSTM1, which is probably one of the most recognized ones (called PDB type 3, OMIM 167250). Mutations in this gene lead to nearly fifty percent of familial PDB cases and up to fifteen percent of cases with the sporadic form of PDB (Hocking et al., 2002; Phillips et al., 2024). The p62 protein, which SQSTSM1 codes, is critical for osteoclast differentiation and function (Hocking et al., 2002). For PDB, bisphosphonates have been the mainstay of treatment until now, providing excellent inhibition of osteoclastic activity and symptomatic relief of the disease. However, when the diagnosis is late, such treatment cannot reverse already established structural alterations. For this reason, preventive strategies such as genetic diagnosis that allow the identification of susceptible individuals before the clinical onset are more relevant (Gennari et al., 2022; Phillips et al., 2024).

Since the SQSTM1 gene is small and there are mutational hotspots, Sanger sequencing is still helpful as a first test (Phillips et al., 2024). Next-generation sequencing (NGS) is useful in detecting the mutations with non-typical patterns (Banaganapalli et al., 2023; Whyte, 2006). However, NGS produces variants of undetermined significance (VUS) that need to be interpreted by a skilled clinician. According to American College of Medical Genetics and Genomics guidelines, variant classification must integrate bioinformatic evidence, functional data, familial segregation, and phenotypic correlation (Richards et al., 2015). Therefore, NGS is suitable for research and special diagnostics when a large group of risk genes needs to be sequenced. Variants that are benign or likely benign do not affect protein function and are frequently found in the general population. VOUS are commonly reported in NGS, and are an essential challenge for clinicians, who should consider a multimodal approach to take place in interpretation (Richards et al., 2015). Genetic stratification offers a powerful potential for preventive early intervention. Direct relatives of the carriers of SQSTM1 mutations have a seven to ten times greater likelihood of developing PDB (Banaganapalli et al., 2023; Gennari et al., 2022).

Besides genetic information, biochemical parameters remain indispensable for diagnosis and monitoring. The most common marker applied is total ALP concentration, indicating enhanced bone turnover. However, because of its non-skeletal sources, its specificity is limited. Blood levels of bone-specific alkaline phosphatase (BSALP) and procollagen type I N-terminal propeptide (P1NP) are more specific for bone formation. A meta-analysis of seventeen studies involving over nine hundred and fifty PDB patients confirmed strong correlations between these markers with scintigraphic parameters of disease activity and therapeutic response (Al Nofal et al., 2015). Detection of mutation carriers allows early surveillance by biochemical testing and scintigraphic imaging every two to three years, resulting in treatment before irreversible changes take place.

Bone scintigraphy with technetium-99m methylene diphosphonate (99mTc-MDP) is the most sensitive technique that can detect metabolically active lesions at an early stage. It is instrumental in asymptomatic carriers, where structural changes may not yet be visible on X-ray. Plain radiographs can detect the presence of typical features, such as trabecular thickening and cortical expansion, but they are less sensitive than other methods in early stages (Banaganapalli et al., 2023; Gennari et al., 2004). CT scans are helpful for surgical planning and fracture evaluation, and MRI is preferentially used to detect complications such as compression of nerves and suspected sarcomatous transformation (Gennari et al., 2004). Table 1 summarizes the molecular and clinical tools in the diagnosis of PDB.

Table 1: Summary of molecular and clinical tools in PDB diagnosis and risk stratification.

Method	Key Characteristics / Role
Sanger sequencing	Gold standard for targeted detection of known SQSTM1 mutations; cost-effective and accurate; best for small genes with mutational hotspots
Next-generation sequencing (NGS)	Allows analysis of multiple genes (TNFRSF11A, VCP, ZNF687); useful in atypical or mutation-negative cases; may detect VUS
Alkaline phosphatase (ALP)	Common biochemical marker of bone turnover; limited specificity due to non-skeletal sources
Bone-specific ALP (BSALP), P1NP	More specific markers of bone formation; correlate well with disease activity and therapy response
Bone scintigraphy (99mTc-MDP)	Highly sensitive for early detection of metabolic lesions; especially useful in asymptomatic mutation carriers
X-ray / Radiographs	Shows classic features (trabecular thickening, cortical expansion); less sensitive in early disease
CT and MRI	CT for surgical planning and fracture analysis; MRI for complications like neural compression or malignancy

The choice of a proper diagnostic tool is the first step in the management of monogenic bone diseases. It moves the therapeutic methods towards individualized, pre-symptomatic care, which could significantly increase treatment outcomes (Gennari et al., 2022; Phillips et al., 2024). Genetic counselling remains an essential measure in the course of PDB. It helps patients to manage the psychological impact of positive testing results, especially in pediatric and asymptomatic adult mutation carriers (Richards et al., 2015).

The diagnostic and prognostic landscape of PDB has dramatically changed during the last twenty years as a result of advances in molecular genetics, biomonitoring, and imaging. In familial PDB type 3, genetic testing is crucial for early identification of high-risk individuals and the implementation of personalized care strategies.

The ZiPP study is a landmark study in the history of intervention for monogenic skeletal diseases. It provides the first clinical trial-based evidence for genotype-driven pharmacological prevention in PDB. Before this, treatment strategies were largely reactive, implemented frequently only post-clinical diagnosis, often after irreversible structural changes had already occurred. The ZiPP trial revolutionized this concept by investigating whether pre-symptomatic therapeutic intervention in genetically susceptible individuals could have a preventative or delaying effect in the course of disease (Phillips et al., 2024).

Participants were monitored for twenty-four months, with several outcomes measuring radiological, biochemical, and clinical endpoints (Phillips et al., 2024).

Although most participants stayed asymptomatic, both laboratory tests and imaging showed that the disease was still active at a subclinical level, and the intervention had an effect (Phillips et al., 2024).

Zoledronic acid (ZA) binds strongly to bone and blocks an enzyme called farnesyl pyrophosphate synthase. This enzyme is involved in the mevalonate pathway and is essential for osteoclast function. That way, it slows down bone resorption, helps stabilize the skeleton, and brings turnover markers back to normal, which fits the biology of PDB (Gennari et al., 2004; Ralston, 2020).

The typical duration of the disease is over several decades, and it is unknown whether a single ZA dose confers long-term protection or whether repeated dosing is necessary. While not surprising, the low rate of obvious clinical progression throughout the study reduces the potential for assessment of long-term functional effects (Visconti et al., 2010; Yang et al., 2021).

For all that, the ZiPP study establishes a clear proof of principle for prophylactic bisphosphonates in monogenic skeletal disease, in doing so, shifting the goalposts for what we define as "treatment" in a condition conventionally treated after clinical manifestation. It also underscores the increased importance of genetic diagnostics as an entry point to personalized preventive medicine, in harmony with approaches that are now being increasingly recognized in the fields of oncology, cardiology, and metabolic rare diseases (Banaganapalli et al., 2023; Gennari et al., 2022; Phillips et al., 2024).

4. DISCUSSION

For people who have been diagnosed with PDB type 3 or for patients with complications, the effects of the disease can be severe. Surgical interventions and long-term rehabilitation may be necessary in some cases. That is why figuring out who might be at higher

risk early on is getting more attention lately. Current knowledge of the genetics of PDB type 3 and the role of molecular diagnostics is discussed, including a discussion of results and implications of the ZiPP study, which was the first to investigate the role of prophylactic drug treatment in carriers of the SQSTM1 mutation (Visconti et al., 2010; Phillips et al., 2024).

Although genetic diagnosis is an objective and precise method, there are difficulties regarding its use. These include the cost of testing technology, the restricted availability of genetic counselling resources, and the proper identification of the appropriate target population (Dusic et al., 2022; Raspa et al., 2021; Goldin et al., 2025).

Another point of debate is whether early pharmacological intervention might lead to over-treatment of those who would never have developed symptomatic disease. In light of the incomplete penetrance of SQSTM1 mutations and the clinical variability in age of onset and severity, strict stratification based on several factors, including family history, genotype, and possibly polygenic risk scores may be needed to refine future intervention therapies (Hocking et al., 2020; Banaganapalli et al., 2023; Rea et al., 2009).

Testing from PDB3 in other affected families with a proven mutation may be warranted, but testing all Paget's patients, as some authors have suggested, may be unwise and clinically unjustified. As of this writing, genetic testing of the gene is shown in families with a positive history and patients with severe or early disease onset (Cundy et al., 2004; Chamoux et al., 2009; Rendina et al., 2024). Indications must be clinical and familial, and the molecular diagnosis should be done in specialized centers. However, the findings of the ZiPP study could pave the way for treatment, at least for the asymptomatic carriers (Phillips et al., 2024). The ZiPP study could be significant in other diseases, rather than just PDB. In populations affected by other monogenic skeletal diseases, such as osteogenesis imperfecta or familial osteoporosis, it could bring a possible model for studies about early intervention (Gennari et al., 2022). Future studies should examine long-term data from ZiPP to analyze the cost-effectiveness of early treatments. It is equally important to work on clear clinical guidelines for treating people who have the mutations but no symptoms yet (Dusic et al., 2022; Raspa et al., 2021). With the cost of and access to sequencing technology continuing to fall, the implementation of genetics into standard orthopedic and metabolic care is fast becoming more realistic (Goldin et al., 2025; Rendina et al., 2024).

5. CONCLUSION

With advances in molecular genetics, the role of genetic diagnostics increases as a diagnostic and preventive tool. In monogenic diseases such as PDB3, it is feasible to recognize high-risk subjects before any clinical symptoms. This can be used for early monitoring, modification of lifestyle, or restriction of the pharmacological intervention. The identification of mutation carriers permits focused surveillance, including serial biochemical and imaging studies in the setting of PDB. This may delay or prevent the onset of symptoms and their complications. However, there are obstacles to the broad implementation of genetic testing that present challenges to scaling up genetic testing.

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interests, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on reasonable request to the Corresponding Author.

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