# Clinical phenotype of adult offspring carriers of the p.Pro392Leu mutation within the *SQSTM1* gene in Paget's disease of bone

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## ARTICLE INFO

## ABSTRACT

Paget's disease of bone (PDB) is a common chronic bone disorder. In the French-Canadian population, the p.Pro392Leu mutation within the *SQSTM1* gene is involved in 46% of familial forms. In New Zealand, the emergence of PDB in offspring inheriting *SQSTM1* mutations was reported to be delayed by a decade compared to their parents. We aimed at assessing the clinical phenotype of offspring carriers of this mutation in our French-Canadian cohort. We reviewed research records from adult offspring carriers of this mutation aged < 90 years and their affected parents. In parents, we collected data on sex, age at diagnosis, number of affected bones, total serum alkaline phosphatase levels (tALPs) at diagnosis. In offspring, PDB extended phenotype assessment relying on tALPs, bone specific alkaline phosphatase levels (bALPs), procollagen type 1 amino-terminal propeptide (P1NP), whole body bone scan and skull and pelvis radiographs, was performed at inclusion from 1996 to 2009 and updated in 2016 to 2018, if not done during the past 8 years. The results showed that among the 36 offspring with an updated phenotype, four of them developed a clinical phenotype of PDB characterized by monostotic or polyostotic increased bone uptake associated with typical radiographic lesions in the affected sites, representing an incidence of 1.83 per 1000 person-years. Moreover, the age at PDB diagnosis was delayed by at least 10 years in the adult offspring carriers of the p.Pro392Leu mutation *versus* their affected parents. Our findings support the utility of a regular monitoring of the adult offspring without PDB but carriers of this mutation.

## 1. Introduction

Paget's disease of bone (PDB) is a chronic metabolic bone disorder characterized by an increase in bone remodeling (Paget, 1876; Desoutter et al., 2012). PDB is considered as the second most common bone disease after osteoporosis. PDB has become less common and less severe over the past decades in almost all countries known to have had a high prevalence in the past (Guay-Bélanger et al., 2015; van Staa et al., 2002; Corral-Gudino et al., 2013; Tan and Ralston, 2014). This chronic disease can be asymptomatic, but it causes severe disabilities in 30% of patients. The formation of bone is chaotic, of poor quality, more sclerotic than normal, whence a tendency to bone hypertrophy, deformities and fractures (Tan and Ralston, 2014; Cundy, 2018; Cundy and Bolland, 2008). PDB is diagnosed by standard radiographs of affected bone sites displayed by a hyperfixation at the whole-body bone scan, which is the most sensitive test for the detection of active pagetic lesions (Seton, 2013; Ferraz-de-Souza and Correa, 2013). The etiology of the disease is still incompletely understood, but in one third of patients with PDB, a familial form inherited in an autosomal dominant pattern with incomplete penetrance can be observed (Johnson-Pais et al., 2003; Merlotti et al., 2005). Several genes have been identified, including the *Sequestosome 1* (*SQSTM1*) gene for which a role in the pathogenesis of PDB was reported (Ralston and Layfield, 2012; Vallet and Ralston, 2016; Michou et al., 2006). This gene encodes for the protein named p62, which is involved in the NF-κB signaling pathway, apoptosis, Nrf2 activation and macro-autophagy (Geetha et al., 2012; Rea et al., 2014). Several mutations in the exons of the *SQSTM1* gene encoding the UBA domain have been linked to PDB. The most common is the p.Pro392Leu mutation found in approximately 46% of familial forms in the French-Canadian population (Morissette et al., 2006). The penetrance of this mutation increases with age, reaching up to 80% after 60 years old. It leads to a C/T change in the exon 8 at position

1215 with a substitution of a proline into leucine (Hocking et al., 2002). Initial studies have reported high penetrance, with about 80% of family members inheriting this mutation developing the disease by the age of 70. Mutations in the *SQSTM1* gene were reported in 25 to 50% of the familial forms of PDB and 5 to 15% in sporadic cases. Several previous studies have identified carriers of *SQSTM1* mutations who do not appear to develop PDB based on biochemical screening or bone scintigraphy. Many of these people were aged 60 years and older. Thus, the age-dependent penetrance of *SQSTM1* gene mutations seems to have decreased over time. Cundy et al has identified that in the last generations, the penetrance of the disease has decreased, the phenotype of PDB was attenuated and less extensive, and it was delayed by 10 years. This phenomenon is not related to early recognition of the disease, as the average age at diagnosis has increased steadily. The finding that the prevalence and severity of PDB is apparently declining seems contrary to the idea that PDB is a high-penetrating genetic disorder. In addition, not all carriers of a *SQSTM1* mutation will develop the clinical phenotype of the disease, indicating that one or more additional factors, including age, are necessary for the clinical development of the disease. In New Zealand, the occurrence of PDB in adult offspring inheriting *SQSTM1* mutations was reported to be delayed by a decade compared to their parents (Bolland et al., 2007; Cundy et al., 2015). In our French-Canadian cohort, we noticed that some parents with PDB and carriers of the p.Pro392Leu mutation, had adult offspring carriers the p.Pro392Leu mutation who had not yet developed the clinical phenotype of the disease. The reasons for the delayed penetrance of PDB in these offspring are not known at this time. We hypothesized that in our cohort the development of PDB clinical phenotype in offspring carriers of the p.Pro392Leu mutation might be delayed compared to their affected parents. In this study, we aimed at assessing the clinical phenotype of offspring carriers of this mutation in our French-Canadian cohort.

## 2. Material and methods

### 2.1. Study population

This study was approved by the CHU de Québec-Université Laval Ethics Committee and all participants signed a consent form before inclusion in the study. Among our 16 large French-Canadian families of PDB linked to the *SQSTM1* gene mutation, we assessed the clinical phenotype of 56 affected parent carriers of the p.Pro392Leu mutation. At inclusion, between 1996 and 2009, we identified 102 adult offspring without PDB carriers of the p.Pro392Leu mutation and aged below 90 years old. Among these 102 participants, only 94 of them had a first clinical phenotyping at inclusion, and in 36 of them an update of the clinical phenotyping was performed between 2016 and 2018 (Fig. 1). Our statistical analyses were based on 14 of these families with an average of 3 individuals per family.

### 2.2. Clinical phenotype assessment of offspring and their affected parents

As reported by Laurin et al., the criteria for the positive diagnosis of PDB were abnormal bone characteristics with monostotic or polyostotic increased bone uptake associated with typical radiographic lesions in the affected sites (Laurin et al., 2001). To define a pagetic clinical phenotype in this study, we used the definition proposed by Laurin et al. In adult offspring without PDB carriers of the p.Pro392Leu mutation, a complete clinical phenotyping (bone scan, standard skull and pelvis radiographs and total serum alkaline phosphatase levels (tALPs)) was performed at baseline, followed by a comparison to their respective affected parents. For each adult offspring without PDB carriers of the p.Pro392Leu mutation, the clinical phenotype update relied on standard radiographs of the skull and pelvis, as well as whole body bone scan using 99mTc-Methyl diphosphonate for all participants for whom it had not been done over the last 8 years. For a more accurate assessment of biochemical markers of bone remodeling, three

biochemical markers were also assayed in serum at the department of biochemistry, CHUM, Montreal, QC, Canada. Bone specific alkaline phosphatase levels (bALPs) and tALPs were assayed using commercial Beckman Coulter commercial kits with the AU5800 (tALPs) and UniCel DxI 800 Access Immunoassay (bALPs) analyzers following manufacturer instructions. Procollagen type 1 amino-terminal propeptide (P1NP) were measured using commercial Roche Diagnostics Kits with the Cobas e411 system. Among these biochemical markers, tALPs (normal range of 30–116 U/L), bALPs (normal range of 3.70–20.90 U/L), and P1NP (normal range of 15.1–73.9 ng/mL) were measured. All these biomarkers were expressed as the number of times to the midpoint of normal range. Self-reported tobacco exposure, wood heating exposure, measles virus infection and measles virus immunization were retrieved from our database for some offspring. The main clinical characteristics of affected parents with PDB and offspring at baseline included sex, age at diagnosis, tALPs, whole body bone scan and radiograph results, and for the affected parents the number of affected bones.

To compare the extent of the disease between affected parents and their offspring, we compared the data of the offspring who developed the disease to those of their respective affected parents. The survival curve was generated to assess the difference between the age of positive bone scan and/or radiograph in affected parents *versus* their offspring.

### 2.3. Statistical analyses

All categorical variables were presented as a frequency and percentage excluding missing values and analyzed using the Pearson exact Chi-Square test. Continuous variables were presented as median and interquartile range (IQR) or mean ± standard deviation (SD), and analyzed using the Wilcoxon-Mann-Whitney test. The Kaplan-Meier survival analysis was performed with the age at positive bone scan and/or radiograph as time-to-event variable. Gray's test was used to evaluate the equality of cumulative incidence functions between parents and offspring. The incidence rate with 95% confidence intervals was estimated by Poisson regression modeling after exclusion of overdispersion problems. We compared socio-demographic characteristics and environmental exposures of offspring with an emergent PDB to offspring without PDB carriers of the *SQSTM1* mutation. We also compared main clinical characteristics of PDB in offspring with emergent PDB to their affected parents. Statistical analyses were performed by the use of SAS version 9.4. The level of significance was set at $p < 0.05$.

## 3. Results

### 3.1. Descriptive analyses at the first phenotype assessment (1996–2009) and at the time of the update (2016–2018) of the clinical phenotype of the offspring without PDB carriers of the mutation, and description of the clinical phenotype of their affected parents

At the time of the first phenotyping, we assessed the clinical phenotype of 94 offspring *versus* 36 in the update, with a median duration of 21 years [20; 36] between the two assessments. Contrary to the first phenotype assessment, in the update, more women were assessed (19 (52.8%) *versus* 17 (47.2%)). The tALPs increased in 9 (25.7%) offspring at the time of the update *versus* at the first assessment but remained in the normal range. Among the affected parents, there were more men than women (33 (62%) men *versus* 21 (38%) women), and the median age at diagnosis was 60 years [50; 68]. The median tALPs was 3.78 [2.07; 8.18] times higher than the midpoint of the normal range and the median number of affected bones was 6 [3; 8]. The number of offspring for each affected parent ranged from 1 to 19 with a median of 6 [4; 8]. Seven (14%) affected parents had at least one offspring with PDB.
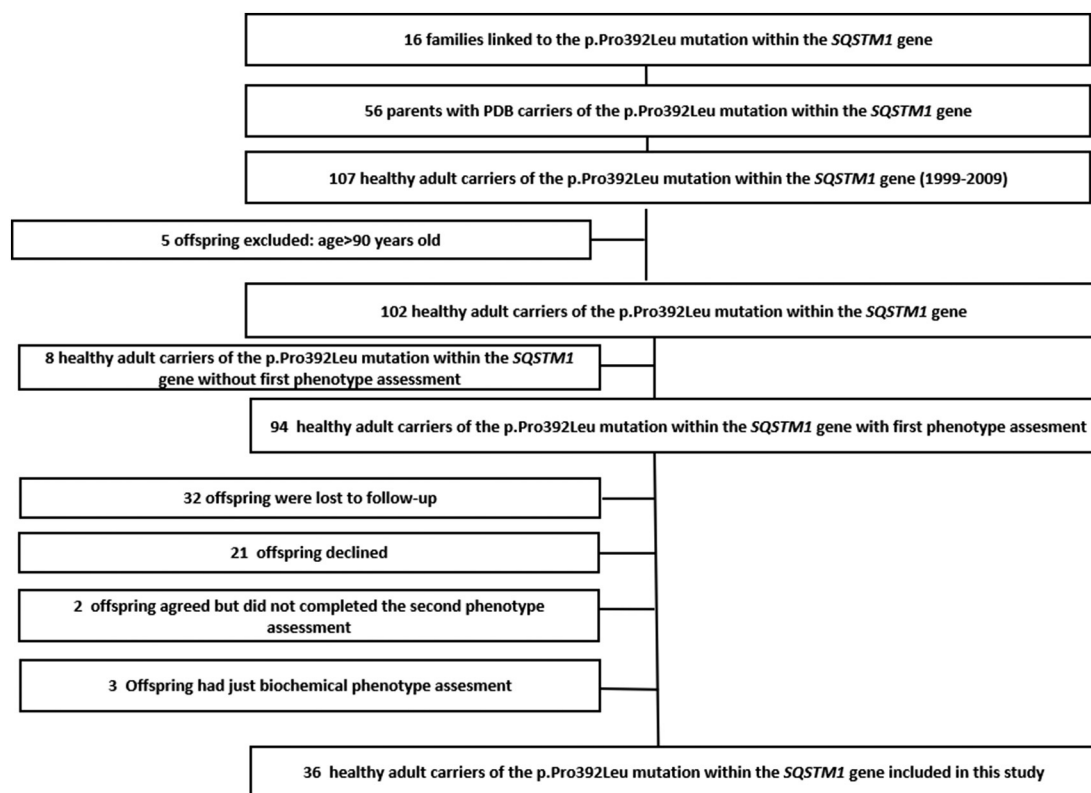
**Fig. 1.** Study design: analysis of 56 parents with PDB from 16 large families and their adult offspring without PDB carriers of the p.Pro392Leu mutation. Data collection from 94 offspring without PDB carriers of the mutation at inclusion between 1996 and 2009, and in 36 of them, an update of the clinical phenotype assessment was performed between 2016 and 2018. Five offspring aged over 90 years were excluded from this update.

### 3.2. Comparison of adult offspring carriers of the p.Pro392Leu mutation who develop PDB during the follow-up to offspring without PDB carriers of the mutation

According to our definition of an emerging PDB, only four out of 36 offspring had a clinical phenotype of PDB. They were all women ($p = 0.1$), with a median age of 64 [55; 75] years old, representing an incidence of 1.83 per 1000 person-years. These women had positive bone scan and typical aspect on skull or pelvis radiographs. One of them had polyostotic involvement (pelvis and right femur) whereas the three others had a monostostic PDB. Their level of bALPs and P1NP were significantly higher when compared to offspring without any clinical phenotype of PDB ($p = 0.02$). Among the four offspring who developed PDB, 66.7% (2/3) were passive smokers ($p = 0.04$) and 100% (3/3) were exposed to wood heating smoke in childhood ($p = 0.07$) (Table 1).

Eight offspring were found to have elevated biochemical markers: five had an increased level of tALPs between inclusion and update of the phenotype, one had high level of P1NP alone, two others had both high level of P1NP and increased level of tALPs, but none of them had a bone scan or radiograph suggestive of PDB.

### 3.3. Comparison of offspring with PDB to their affected parents

All offspring with an emerging PDB and three affected parents were women. The number of affected bones and tALPs levels were significantly higher in the affected parents than offspring with PDB, respectively ($p = 0.02$ and $p = 0.04$) (Table 2).

The age at PDB diagnosis was significantly delayed in the offspring carriers of the mutation compared to their affected parents ($p < 0.0001$) (Fig. 2). The occurrence of the disease in the offspring was delayed by at least 10 years *versus* their affected parents.

### 4. Discussion

In this study, after 21 years [20; 36] of follow-up, four adult offspring carriers of the p.Pro392Leu mutation within the *SQSTM1* gene developed a clinical phenotype of PDB. Eight additional offspring had elevated bone biomarkers but without any bone abnormality on bone imaging. The levels of bALPs and P1NP were higher among offspring with an emerging PDB than in offspring without PDB carriers of the *SQSTM1* mutation. The number of affected bones and the levels of tALPs were significantly higher in the affected parents than in their affected offspring. The age at PDB diagnosis was delayed by at least 10 years in offspring compared to their affected parents, with less severe activity and bone extent of the disease. Among bone biomarkers (tALPs, bALPs, and P1NP) measured in this study, P1NP was the most frequently positive test in our cohort. Concerning tobacco and wood heating smoke exposure, 10 out of 20 offspring were exposed to cigarette smoke and 11 out of 20 were exposed to wood heating. Among the four offspring who developed the disease, 2 were exposed to cigarette smoke as passive smokers and 3 were exposed to wood heating smoke during childhood. Concerning measles virus, 8 out of 14 offspring self-reported having been infected by measles virus and 4 out of 11 self-reported a measles virus immunization. Among the four offspring who developed the disease, two reported measles virus infection, and none of them had immunization against measles virus.

Cundy et al. reported two patients who developed PDB among 28 carriers of a mutation in the *SQSTM1* gene after a follow-up of 5.1 years [3.7; 6.3], representing an incidence rate of 5 per 51 patient-years - or one case per 10 patient-years in the specific age group of 46 to 51 years old (Cundy et al., 2015). In a 16-year period of follow-up in a Dutch cohort, one (12.5%) carrier of a mutation within the *SQSTM1* gene developed the disease, but the bone scan was performed in this study only in participants who had raised levels of ALP or P1NP or both (Peeters et al., 2019). The recent study of Cronin et al. reported 20

**Table 1**

Comparison of offspring who develop PDB during the follow-up to offspring without PDB carriers of the *SQSTM1* mutation after updated phenotype assessment.

| Variables | | Updated phenotype assessment | | |
|---|---|---|---|---|
| | | Offspring without PDB ($N = 32$) | Offspring with PDB ($N = 4$) | *p*-Value |
| Age in years, median (IQR)[b] | | 64(59;69) | 65 (55;75) | 0.7 |
| Female sex (n)[c] | | 47% (15/32) | 100% (4/4) | 0.10[T] |
| tALPs measurement, median (IQR)[a, b] | | 0.8 (0.7;1) | 0.9 (0.8;1) | 0.15 |
| tALPs interpretation (n/N)[c] | Elevated | 22% (7/32) | 67% (2/3) | 0.15 |
| bALPs measurement, median (IQR)[a, b] | | 0.9 (0.9;1.2) | 1.2 (1.1;1.3) | 0.02* |
| bALPs Interpretation, (n/N)[c] | Elevated | 3.4% (1/29) | 0% (0/4) | 1 |
| P1NP measurement, median (IQR)[a, b] | | 1.2 (1.;1.5) | 2.2 (1.7;2.7) | 0.02* |
| P1NP interpretation (n/N)[c] | Elevated | 10% (3/29) | 75% (3/4) | 0.01* |
| Bone scan (n/N)[c] | Abnormal | 0% (0/32) | 50% (2/4) | |
| Radiographs (skull, pelvis), (n/N)[c] | Abnormal | 0% (0/29) | 100% (4/4) | |
| Smoker (n/N)[c] | Yes | 53% (9/17) | 33% (1/3) | 1 |
| Passive smoker, (n/N)[c] | Yes | 6% (1/17) | 67% (2/3) | 0.04* |
| Wood Heating exposure (n/N)[c] | Yes | 47% (8/17) | 100% (3/3) | 0.22 |
| Wood heating exposure in childhood, (n/N)[c] | Yes | 35% (6/17) | 100% (3/3) | 0.07[T] |
| Measles virus infection (n/N)[c] | Yes | 50% (6/12) | 100% (2/2) | 0.47 |
| Measles virus immunization (n/N)[c] | Yes | 44% (4/9) | 0% (0/2) | 0.49 |

n: number of participants, N: total number of participant.

[a] Level expressed as the number of times the midpoint of normal range.
[b] Wilcoxon Mann Whitney test.
[c] Exact Pearson Chi square test;
* < 0.05.
[T] < 0.15.

participants (9%) carriers of a *SQSTM1* mutation with asymptomatic PDB, based on bone scan only as radiographs of bones displaying uptake on bone scan were not performed in this study (Cronin et al., 2020) (Table 3).

In the literature, in recent decades, the prevalence and the clinical severity of PDB were reported to have declined rapidly in some countries such as New Zealand, Spain and the United Kingdom (Corral-Gudino et al., 2013). These epidemiological changes may have contributed to the low incidence rate of clinical phenotype of PDB observed in the offspring carriers of the p.Pro392Leu mutation in this study, as well as the delayed age at PDB diagnosis of offspring *versus* their affected parents.

In our study, we indeed observed a less severe activity and bone extent of the disease and a delayed age at PDB diagnosis by at least 10 years in offspring compared to their affected parents, which is consistent with an age at diagnosis delayed by 10 years as reported in the literature (Bolland et al., 2007). This rapid change could be explained by modifications in the exposure to one or more environmental factors. Several environmental factors have been associated with PDB such as dietary deficiencies (calcium or vitamin D deficiency in childhood), exposure to combustion products, rural lifestyle, or contact with domestic animals (Vallet and Ralston, 2016; Galson and Roodman, 2014). Chronic infection by the measles virus may contribute to the pagetic phenotype of osteoclasts by contributing to osteoclastic hypermultinucleation, expression of TAF-12 and susceptibility to IL-6 production (Galson and Roodman, 2014; Singer, 2015; Teramachi et al., 2016; Chung and Van Hul, 2012), although the role of measles virus in PDB pathogenesis remains controversial in the literature.

A previous study in our French-Canadian cohort suggested that indoor air pollutants such as tobacco smoke may contribute to PDB pathogenesis (Numan et al., 2019). Moreover, Audet et al. found an association of PDB in the French-Canadian cohort with wood fire heating in childhood and/or adolescence but no association with measles immunization or childhood sickness (Audet et al., 2017). Some studies have identified *SQSTM1* mutation carriers that do not have the clinical phenotype of PDB based on biochemical screening or bone scan. Many of these individuals are under the age of 55, but the penetrance of *SQSTM1* mutations is largely age-dependent (Bolland et al., 2007), stressing the importance of a regular follow-up of adult offspring carriers of the p.Pro392Leu mutation within the *SQSTM1* gene. Our results reinforced the utility of standard radiographs of the most frequently affected bone sites for the clinical phenotype assessment of PDB. The measure of biochemical markers of bone remodeling, including tALPs, is very useful in clinical practice to monitor the activity of PDB, but this marker is not specific to the disease. Other bone biomarkers, such as the serum C-terminal telopeptide (CTX), the N-terminal telopeptide (NTX), and the P1NP, the latter being not available in clinical practice, also have a clinical utility at evaluating the activity of PDB (Seton, 2013; Ferraz-de-Souza and Correa, 2013).

Although we investigated 16 large families with 94 offspring at inclusion (1996–2009), the small number of participants to the clinical phenotype update, with only 36 offspring, represents a study limitation. The high cost of the tests for the clinical phenotyping prevented us from investigating family members who were not carriers of the p.Pro392Leu mutation. However, this study allowed us to highlight the importance of a follow-up in the adult offspring without PDB carriers of the

**Table 2**

Comparison between offspring with an emerging PDB and their affected parents.

| Variables | Affected parent | Affected offspring | P-value |
|---|---|---|---|
| Age at diagnosis in years, Mean ± SD | 63 ± 5 | 64 ± 11 | 0.93 |
| Number of affected bones, Mean ± SD | 7 ± 2 | 1 ± 0 | 0.02* |
| tALPs measurement[a], Mean ± SD | 3 ± 1 | 1 ± 0.1 | 0.04* |

*T* < 0.15.
[a] Level expressed as the number of times the midpoint of normal range, student *t*-test.
* < 0.05.

**Cumulative Incidence Functions**
With 95% Confidence Limits
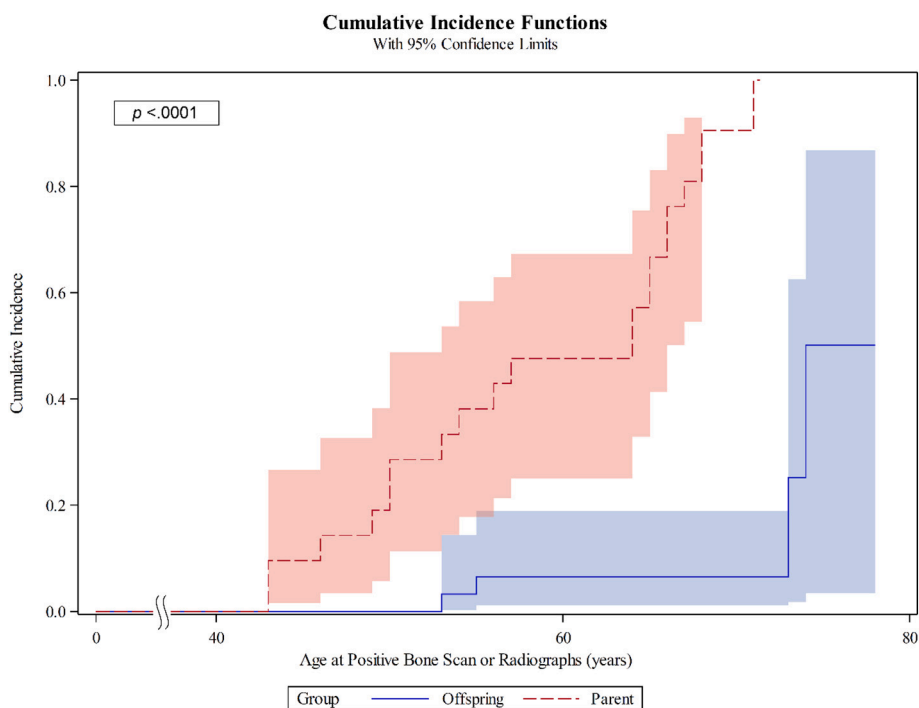


**Fig. 2.** Comparison of the age at PDB diagnosis in offspring with an emerging clinical phenotype of PDB and carriers of the p.Pro392Leu mutation, with their affected parents, by cumulative incidence function estimation using Kaplan-Meier analysis.

**Table 3**
Offspring carriers of a *SQSTM1* mutation who developed an emerging PDB in this study and in the literature.

| Proportion of offspring with an emerging Paget's disease | Follow-up duration | Mean age at diagnosis (years) | Criteria for a positive diagnosis of PDB | References |
|---|---|---|---|---|
| 4/36 | 21 years | 65 ± 12 | Monostotic or polyostotic increased bone uptake on scintiscan associated with typical radiographic lesions in the affected sites | Our study |
| 4/23 | – | 45 ± 5 | Scintiscan | Bolland et al., 2007 |
| 2/28 | 5.1 years | 48 ± 7 | Scintigraphic appearances of PDB coupled with characteristic radiographic changes or ALP increase (or both) | Cundy et al., 2015 |
| 1/61 | 16 years | 74 ± 0 | Bone scan performed only in participants who had raised levels of ALP or PINP or both | Peeters et al., 2019 |
| 20/222 | – | 54 ± 9 | Scintiscan | Cronin et al., 2020 |

p.Pro392Leu mutation. Considering the results presented in this study and as an expert opinion on a topic where no data are available in the literature, a follow-up by bone scan might be considered after the age of 60, and every 10 years thereafter up to age 80.

## CRediT authorship contribution statement

Study design: LM, JPB. Patient recruitment and acquisition of data: LM, JPB, EG, FJG, MD, EG, AS. Analysis and interpretation of data: LM, JPB, EG, FJG, MD, EG, AS, GG, DS. Revision of manuscript content (all authors). Approving final version of manuscript (all authors). LM takes responsibility for the integrity of the data analysis.

## Transparency document

The Transparency document associated with this article can be found, in online version.

## Declaration of competing interest

The authors have nothing to disclose.

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