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Research Article

Development of Paget's disease of bone in adults inheriting *SQSTM1* mutations: a long-term follow-up

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Abstract

In a 2015 study of *SQSTM1* mutation carriers who had initial negative bone scintigraphy, we found that the rate of development of Paget's disease of bone (PDB) over 5 yr was low. We report here an additional 8-yr follow-up of this cohort, exploring the hypothesis that the rate of development of PDB would increase as the cohort aged. In the current study, 21 of 24 subjects from 2015 who had a negative bone scintiscan at baseline and at first follow-up, had a repeat scintiscan and measurement of total serum alkaline phosphatase activity. Two subjects with P392L mutations were identified as having PDB (monostotic in one case, 2 bones involved in the other), giving an incidence during this follow-up period of 1 per 87 patient years or 11.9 per 1000 patient years. This was contrary to our hypothesis, as the rate of development had decreased as the cohort aged. When we compared by survival analysis the age at presentation with symptomatic PDB in the older generation, we found that the age of onset was later and disease severity in the affected relatives was markedly less than in their clinically affected parents ($p < .001$). Our results are in keeping with other recently published studies and the general secular trend in PDB and support the idea that an important environmental-genetic interaction is involved with the development of PDB and that exposure to the putative environmental factor has substantially reduced.

Keywords: metabolic bone disease, Paget's disease, sequestosome mutation, rate of development, environmental-genetic interaction

Lay Summary

Paget's disease of bone (PDB) affects older adults and may cause problems, such as fracture, arthritis, and deafness. We studied individuals who had inherited a genetic mutation associated with PDB to determine whether they would develop the condition. In an earlier study, few had developed PDB, but we hypothesized that the rate at which PDB develops would increase as the cohort aged, but this was not the case. Our results agree with other studies and support the idea that PDB results from both an inherited tendency and an environmental component and that exposure to the environmental factor has diminished substantially.

Introduction

Paget's disease of the bone (PDB) is a focal bone disorder characterized by increased bone resorption and disorganized bone formation. It typically affects older adults and may lead to complications, such as bone deformity, fracture, secondary osteoarthritis, and deafness. The cause of PDB remains uncertain, but there is evidence of genetic predisposition. Mutations in various genes, including *VCP*, *ZNF68*, *PFN1*, *HNRNPA2B1*, and *HNRNPA1* have all been associated with familial PDB, but the gene most commonly implicated is *SQSTM1*.[1,2] Over 30 different mutations in *SQSTM1* have been associated with familial PDB and a smaller proportion of non-familial cases. Although there is an undoubted genetic predisposition, there has been a strong secular trend of PDB being diagnosed later in life and with less extensive disease than formerly, suggesting an important (and changing) environmental component to its cause.[3–7]

In 2007, we reported a study of 23 adults in their forties who had inherited *SQSTM1* mutations from clinically affected parents and underwent skeletal scintigraphy, which is considered the most sensitive method of detecting and quantitating PDB. The majority showed no sign of PDB, but the 4 that had developed PDB did so later in life and had less extensive disease than their affected parent.[8] In a 2015 study of 26 *SQSTM1* mutation carriers who had initial negative bone scintigraphy, we found that the rate of development of PDB over 5 yr was low.[9] However, as PDB becomes more prevalent with age,[10] we anticipated that additional cases would emerge with time. We report here an additional 8-yr follow-up of this cohort, exploring the hypothesis that the rate of development of PDB would increase as the cohort aged.

Materials and methods

Study population

The original and follow-up study populations are as previously reported,[8,9] and their relations with the current study are shown in Figure 1. Twenty-six participants were recruited into the initial follow-up study, of whom 2 were identified as having Paget's disease. The remaining 24 subjects were contacted to participate in a further follow-up study. Of these, 1 was not contactable, 1 declined to participate, and 1 did

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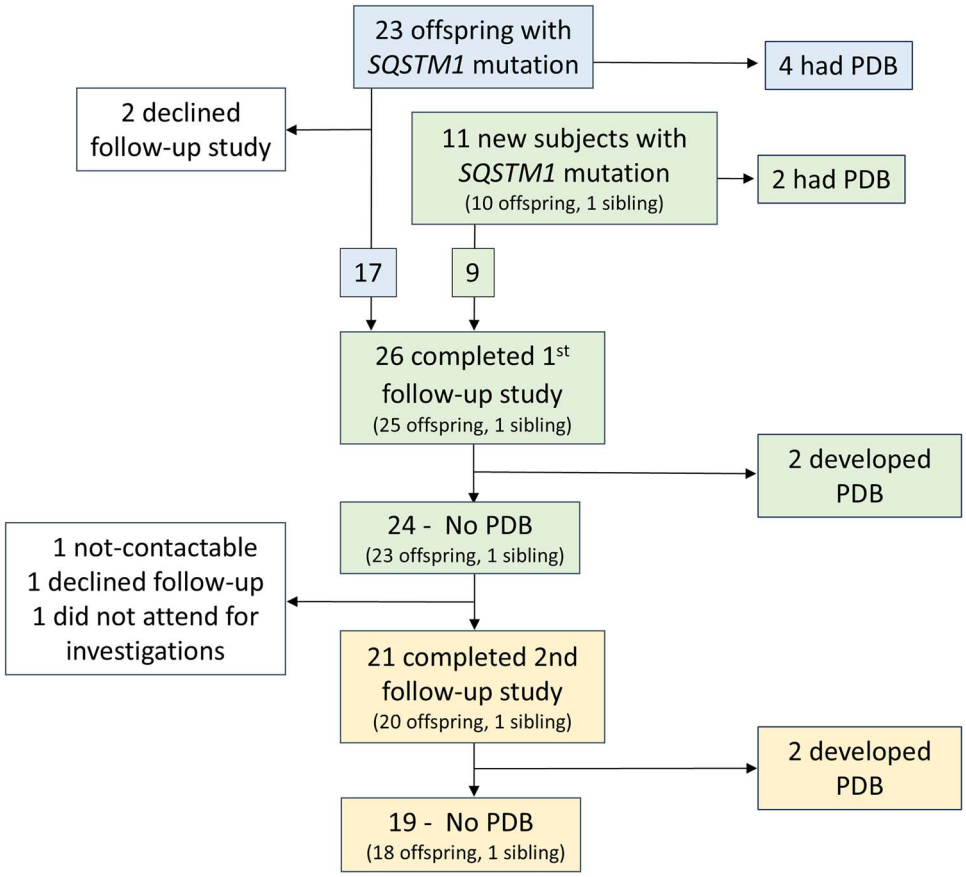

Figure 1. Structure of the study and its relation to our previous studies. Blue shaded boxes: 23 people took part in our 2007 study.[8] Green shaded boxes: The 26 people with initial negative bone scinticans reported in our 2015 study.[9] Yellow shaded boxes: This study 21 people without Paget's disease had a second bone scintiscan a mean 8.3 yr after the first follow-up scan (13.5 yr after baseline scan).

not attend for investigations. Thus, 21 of 24 subjects (88%) participated in and completed the current study (Figure 1).

Study design

Each of these 21 *SQSTM1* mutation-positive subjects had a negative bone scintiscan at baseline and at first follow-up (mean 5.1 yr after baseline scan). Repeat scintiscans using ^{99}Tc-labeled methylene bisphosphonate were obtained, and radiographs were taken of any areas of increased isotope uptake that were suggestive of possible pagetic involvement. Paget's disease was deemed to be present if there were characteristic scintigraphic features together with a diagnostic radiographic appearance of the bone(s) identified on the scintiscan. Total serum alkaline phosphatase (ALP) activity was measured on an autoanalyzer according to the standard method of the subject's local laboratory, and results were compared to the assay-specific normal range. In those offspring found to have PDB in the previous and current follow-up studies, we compared disease extent and ALP levels at diagnosis with those of their affected parent. Disease extent was calculated from the scintiscan using the method of Coutris et al.[11] To provide an updated assessment of the delay in the development of PDB relative to their clinically diagnosed parents, we repeated the comparison made in our 2015 study. In this, we compared by survival analysis the age at presentation with symptomatic PDB in the older generation ($n = 21$) with the age at diagnosis by scintigraphy in their asymptomatic first-degree relatives using the combined cohort ($n = 34$; 33 adult offspring, 1 sibling) described in our earlier papers.[8,9]

Statistical analysis

Comparisons were made between groups for continuous variables using Mann–Whitney test for nonparametric data. Comparisons of multiple time points were made using a one-way analysis of variance (ANOVA). Kaplan–Meier survival analysis was used to compare the age at diagnosis of Paget's disease between groups. The statistical tests were undertaken using GraphPad Prism version 5.02 for Windows (GraphPad Software, San Diego, CA, USA). $p < .05$ was considered statistically significant; all tests were two-tailed. 95% confidence intervals (CI) were calculated using OpenEpi.

All participants gave written, informed consent, and the study was approved by the local ethics committee. The study was registered at the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), registration number ACTRN12605000294651.

Results

Twenty-one previously unaffected subjects (15 women, 6 men; mean age 59 [range 48-77] yr) had further skeletal scintigraphy a mean 8.3 yr after the second scan (range 70-142 mo) and a mean 13.5 yr after the first scan (range 118-186 mo). ALP activity was measured within an average of 4 (range 0-22) mo

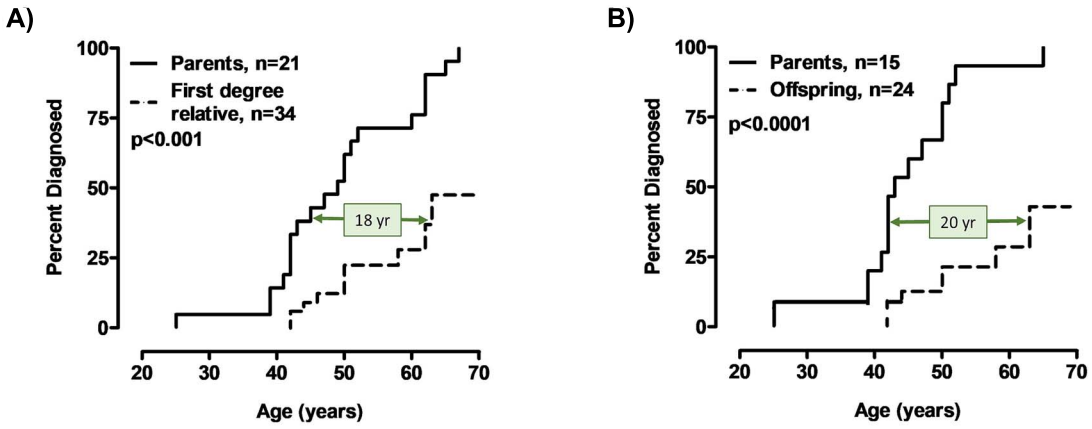

Figure 2. Kaplan–Meier plots showing the emergence of Paget's disease with increasing age. Left: Comparison of 34 first-degree relatives (33 offspring, 1 sibling, born between 1942 and 1976) with their 21 clinically affected parent or sibling (born between 1917 and 1950). The 34 subjects comprise 23 reported in our 2007 study and 11 additional subjects recruited into our 2015 study (see Figure 1). Right: Comparison of 24 offspring (born between 1950 and 1967) who were older at the time of study than were their 15 affected parents (born between 1917 and 1946) at the time of clinical diagnosis. Note the 18-20 yr delay in the scintigraphic detection of PDB compared to the clinically affected older group.

of the scintiscan in each subject. All subjects carried heterozygous *SQSTM1* mutations (P392L in 16 people, E396X in 2, G411S in 3).

Two subjects with P392L mutations were identified as having PDB giving an incidence during this follow-up period of 1 per 87 patient years or 11.9 per 1000 patient-years. The first was a 58-yr-old man with Paget's disease affecting the right tibia and ulna on scintigraphy and confirmed by radiography. He was asymptomatic, and his ALP levels were within the normal range, with no increase since baseline or the previous assessment. The second was a 63-yr-old woman whose scintigraphy showed PDB in her sacrum and was confirmed by radiography. She was asymptomatic, and her bone-specific ALP (bSALP) was in the normal range. A different measure of ALP was used in her case; it could not be compared to previous levels. The age at which PDB was diagnosed was greater than that of the 2 clinically identified probands (2 parents) (58 vs 51 yr and 63 vs 50 yr, respectively), and both had significantly less extensive disease as judged by the number of bones affected (2 vs 7 and 1 vs 4) and the proportion of the skeleton involved (6 vs 23% and 5 vs 9%, respectively).

In the updated survival analysis, we compared the age at which PDB was diagnosed clinically in 21 identified probands (20 parents, one sibling) with the age at which PDB was diagnosed by scintigraphy in 34 of their first-degree relatives (Figure 1) who had inherited the same *SQSTM1* mutation. The age of diagnosis was significantly greater in the first-degree relatives ($p < .0001$, Figure 2A). This difference was more marked in adult offspring who were older at the time of the study than their affected parents were at the time of clinical diagnosis ($p < .0001$, Figure 2B). The disease activity was significantly higher in the affected parents compared to their offspring as judged by ALP activity, the number of bones affected, and the proportion of the skeleton involved (all $p < .005$; Table 1).

Discussion

In this long-term follow-up study, we confirmed the low rate of emergence of PDB in adult offspring carriers of mutations in *SQSTM1*. Our hypothesis that the rate of development of PDB in this cohort would increase as the cohort aged was not supported by our findings. In the original 5-yr follow-up,[9] the rate was 1 new case per 67 patient-years (between age 46 and 51 yr), whereas the rate in the subsequent follow-up had lengthened to 1 new case per 87 patient-years (between age 51 and 59 yr). These rates are considerably lower than the estimated incidence in the probands' parents over a similar time period (7 per 162 patient years, or 1 case per 23 patient-years).

Two similar studies have been published recently, and the control arm of the ZiPP study also provides valuable information on the rate at which *SQSTM1* mutation carriers develop PDB.[12–14] These studies show a rate of development of new lesions ranging from 2 to 5 per 1000 patient-years, with an estimated incidence between 1 new case per 189 to 652 patient-years (summarized in Table 2). In the Dutch study,[12] scintiscans were made only if bone turnover markers were raised, so their estimate may be artifactually low. The rates in our New Zealand cohort are actually higher than the other studies, but because rates were low in all the studies, the CIs overlap. The majority of subjects who developed PDB in these studies had monostotic disease, and all were asymptomatic. These results are in keeping with the general secular trend in PDB of cases occurring later in life and with much less extensive disease than formerly—a trend that is happening irrespective of *SQSTM1* mutation status.

In the survival analysis, the age of onset was later, and disease severity in the affected relatives was markedly less than in their clinically affected parents. In both our earlier paper and in the Québec study,[9,13] the age of diagnosis of PDB was delayed by at least 10 yr in the offspring compared to their affected parents. Our updated survival data analysis suggests this may now be an underestimate. As shown in Figure 2A, the age by which a third of each group had developed PDB differed by 20 yr. Given that the affected parents presented with established polyostotic disease, the true difference in age at onset is likely to be even greater. In the placebo arm of the ZiPP study, the rate at which new cases of PDB were detected over an average 6.6-yr follow-up was only one eighth that anticipated when the study was designed, which was the main reason why the primary outcome was not reached.[14] Taken together, these results differ markedly from estimates made

Table 1. Pagetic phenotype of adult offspring compared to their affected parent.

At time of detection of PDB	Affected parent (8 M, 2 F)	Affected offspring (3 M, 7 F)	*p* value*
Age (yr) median (SD)	49 (9)	50 (8)	NS
Year of birth (range)	1917-1942	1950-1962	-
Alkaline phosphatase (IU/L) mean (range)	1250 (209-2850)	121 (78-200)	$p < .0001$
Bones involved (*n*) median (range)	11 (1-43)	1 (1-6)	$p = .0013$
Skeletal involvement (%) median (range)	29 (5.0-63.5)	5 (1-10.5)	$p = .0008$

*Mann–Whitney test. Abbreviation: F, Female; M, Male; PDB, Paget's disease of bone.

Table 2. Summary of reports on the rate of development of new cases of Paget's disease of the bone in *SQSTM1* mutation carriers.

Reference	No. of subjects	Average age (yr)		Average follow-up duration (yr)	New cases (*n*)	Monostotic/ polyostotic disease	Rate of development of new cases*		Note
		at entry	at end				Per 1000 patient-years	Patient-years per case	
Peeters 2019[12]	14	58	74	16	1	1/0	5 (<1-22)	224 (45-4476)	Scintiscans only when turnover markers increased
Dessay 2020[13]	36	44	65	21	4	3/1	5 (2-13)	189 (78-595)	
Phillips 2023[14]	99	50	57	6.6	1	1/0	2 (<1-8)	652 (132-13 026)	
Cundy 2015[9]	26	45	50	5.2	2	2/0	15 (3-49)	67 (20-400)	Same cohort – continued follow-up
This paper 2024	21	51	59	8.3	2	1/1	12 (<1-38)	87 (26-519)	

*95% confidence intervals indicated in brackets.

nearly 20 yr ago that suggested the penetrance of PDB in *SQSTM1* mutation carriers was maximal (79%-87%) from 60 yr of age.[15]

The nature of the putative environmental factor is uncertain, with contributions from zoonosis, exposure to viruses, and environmental pollutants, such as domestic coal use, all theorized as potential causes.[10,16,17] It is possible that this factor exerts its effect through modifier genes that regulate the age and onset of severity of PDB. One of the limitations of our study is that we did not collect data about potential environmental factors and cannot comment on their contribution to the development of PDB in our cohort. Another limitation is the higher number of women than men in the study, which may underestimate the emergence of disease as PDB tends to be more common in men in epidemiologic studies. However, recent data on the incidence of PDB from the UK Clinical Practice Research Datalink suggests the sex difference in incidence does not diverge until age 60.[18] The small number of subjects and our inability to contact all unaffected subjects for follow-up represent other limitations.

In conclusion, we have confirmed that adult offspring with *SQSTM1* mutations develop PDB significantly later than their affected parents, and, if they do so, it is in a markedly attenuated form. We estimate the delay in development may be in the region of 20 yr. Contrary to our hypothesis, the rate of development did not increase as the cohort aged. This is in keeping with similar studies and strongly supports the idea that an important environmental-genetic interaction is involved with the development of PDB. It would be interesting to know if the same secular trend is seen in families carrying mutations in other Paget-related genes, such as *VCP*. While our study shows that a small proportion of *SQSTM1* mutation carriers continue to develop PDB into middle age, it does call into question the value of screening and regular surveillance, given the low incidence and that the disease is generally of limited extent and asymptomatic.

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Study design: T.C. Patient recruitment and acquisition of data: S.O. Analysis of data and interpretation of data: T.C., M.B., S.O. Revision of manuscript content: T.C., M.B., S.O. Approving final version of manuscript: T.C., M.B., S.O.

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Conflicts of interest

None of the authors had a conflict of interest to declare. This study was not supported by any sponsor or funder.

All participants gave written, informed consent, and the study was approved by the local ethics committee. The study was registered at the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), registration number ACTRN12605000294651.

The data that support the findings of this study are available in anonymized form on reasonable request from the corresponding author (S.O.).

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