# An ancient form of Paget's Disease at Norton Priory, UK

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**Funding citation: The authors wish to thank Doreen Beck, the Paget's Association and the Wellcome Trust for funding this research**.

## Introduction

Paget's Disease of Bone (PDB) is a chronic, metabolic disease disrupting normal bone turnover. PDB can be traced within an individual through three stages: an osteoclastic phase comprising of increased bone resorption, followed swiftly by a disordered osteoblastic remodelling phase which leads to a disorganized structures of woven and lamellar bone[1]. Consequently, these advanced changes to the skeletal architecture leads to bone enlargement, fragility and deformity. PDB occurs more commonly in males and in older individuals[2] with a regional concentration in the northwest of England [3,4,], although the prevalence of this disease is higher within the UK in comparison to other countries [5,6,7,8].

Previously, a bone disorder with similarities to modern PDB has been identified in six skeletons from Norton Priory[9]. However, a more recent examination has identified that this disease is far more extensive than previously reported[10]. Burrell et al., (2018) characterised the six skeletons in greater detail and speculate that other affected individuals within the collection may have been overlooked. This paper considers an additional 12 individuals identified with skeletal lesions similar to modern PDB and our results are presented here for the first time.

## Materials and Methods

The studied skeletons are from the Norton Priory Human Skeletal Collection (n=130) housed at the Norton Priory Museum and Gardens in Runcorn, Cheshire, U.K. (Fig. 1). The demographics of this sample are typical of a monastic site with a total of 85 males, 29 females and 16 non-adults [11]. The 12 skeletons included in this paper (9 male and 3 female, between 35-59 years of age) were examined from *head-to-toe* for any distinct macroscopic changes related to PDB (Fig. 2). Once complete, each skeleton was subjected to full radiographic review (Fig. 3). A single tooth was extracted from each skeleton. The tooth roots were submitted for AMS radiocarbon dating and stable isotopic analysis ($^{13}C$ and $^{15}N$) for paleodiet reconstruction. The tooth crowns were submitted to obtain their strontium ($^{87}Sr/^{86}Sr$) and oxygen ($^{18}O$) isotopes values. These analyses are used to estimate their provenance and potential mobility.

Finally, molecular diagnosis of PDB was attempted on 9 skeletons (inclusive of 5 skeletons from the previous study[10]). These paleoproteomic analyses subject petrous and/or teeth samples to sequential extraction with guanidinium hydrochloride buffers using a modification of an established protocol[13]. Revealed extractions are used to catalogue constituent ancient proteins to provide insights into the disease aetiology.

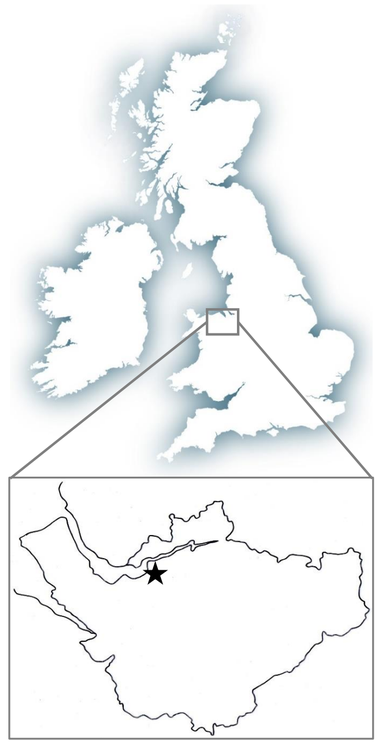


**Figure 1: Map of the U.K. with approximate location of Norton Priory.**



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**Figure 2: Proximal right femur of SK22(Gr21) displaying macroscopic lesions of PDB.**

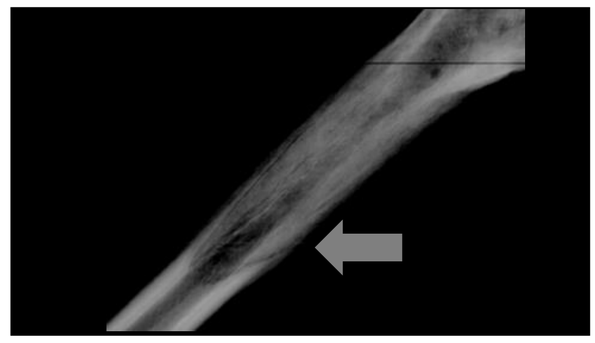


**Figure 3: Radiographic image of proximal right femur of SK22(Gr21) displaying the '*Blade of Grass*' characteristic of PDB.**

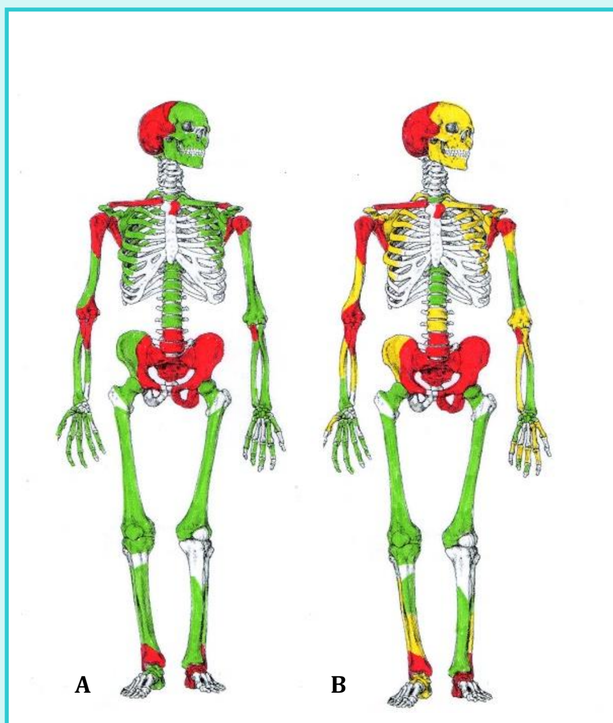



**Figure 4: Macroscopic (a) and radiographic (b) distribution of bones affected with PDB-like changes in SK37(Gr35). Macroscopic changes (highlighted red), internal lytic changes identified during radiographic analysis (highlighted yellow) and unaffected bones (highlighted green).**

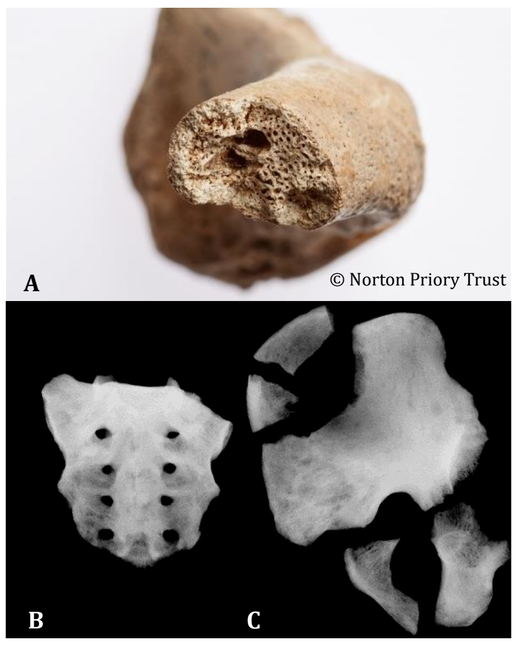



**Figure 5: Macroscopic lesions of PDB observed in the right clavicle (a) and characteristic radiographic features of PDB observed in the sacrum (b) and left pelvis (c) of SK37(Gr35).**

## Results

As a representative example, SK37 (Gr35), an adult male shows distinct porous macroscopic changes across ~40% of his skeleton (see Fig. 4a). Interestingly, the internal structural changes of this disease can be observed in his right clavicle (Fig. 5a). Radiographic imaging has identified characteristic lesions of this disease affecting up to ~75% of his skeleton (see Fig. 4b). For example, the chaotic osteoblastic activity, leading to the development of thickened and enlarged bone can be observed in the left os coxae (Fig. 5b) and sacrum (Fig. 5c). Overall, pathological changes were extensive in the 12 skeletons. Up to 40% of each skeleton displays visual PDB-like lesions, while radiographic analyses reveal that up to 75% of the skeleton is affected in some cases.

Radiocarbon analyses have confirmed that these individuals are medieval in origin. In total, the 12 skeletons cover ca. 400 years of Norton's history (AD 1020 to AD 1479) with some individuals appearing to have lived during the same lifetime. Results of the carbon (δ13C) and nitrogen (δ15N) stable isotopes show high levels of nitrogen, recognising a marine protein in their diet (fish) which is typical of a monastic lifestyle[14,15]. Results of their strontium ($^{87}Sr/^{86}Sr$) and oxygen ($^{18}O$) isotope values identified that they originated and remained to live locally. Inclusive of the original six skeletons[10], these new analyses identify that the new population prevalence is of at *least* 13.8% (18/130) or 15.8% of the adult sample (18/114) in the Norton collection.

Paleoproteomic analysis was successful for 4 of the 9 skeletons sampled. More than 60% of the primary sequence of SQSTM1/p62 (p62) was detected, a protein linked to the familial and sporadic forms of contemporary PDB. Notably, western blotting indicated strong immunoreactive bands migrating with a higher molecular weight than the control band. These observations indicate that the reported protein is a modified and likely ancient precursor of the p62 protein.

## Discussion and Conclusions

This paper provides new information for 12 additional skeletons with PDB-like changes at Norton Priory. The authors have conducted a thorough differential diagnosis of this disease[10]. Although the lesions are characteristic of contemporary PDB, the etiology is a somewhat different. Typically PDB affects the bones of the axial skeleton[16] with one of two bones affected[17] and the Norton skeletons follow this trend. However, radiographic analysis identifies that up to 75% of their skeleton is affected, which is unusually extensive. Comparable archaeological collections such as Barton-on-Humber[18] have reported PDB-like changes at a sample prevalence of ~2% while the current prevalence at Norton is 15.8%. However, this will increase as additional skeletons exhibiting PDB-like changes from Norton are being considered for further review.

Today, PDB is often reported in individuals over 55 years of age and with a higher incidence in males than females[4]. PDB is considered rare in patients under 50 years of age[2]. Here, males dominate the Norton sample but, age-at-death assessments start at 35 years (data not shown). The authors note that age-at-death assessments in adult human skeletal remains is not precise[19]. However, only 5 Norton skeletons were assessed in the highest age-at-death categories (50+ years). As PDB is considered to be a disease of the elderly[2], these results suggest a *possible* early on-set of this disease at Norton. In summary, whilst broadly resembling the skeletal changes seen in contemporary PDB, there are many atypical features within the Norton Priory remains.

The variability of ancient p62 detection in the affected skeletons are likely due to the varied burial conditions at Norton (e.g. stone coffin *vs* shroud). Nonetheless, the successful samples have identified a modified p62 protein in the Norton skeletons suggesting the disease at Norton Priory may have been an ancient precursor of modern day PDB, providing new insight to the atypical etiology observed at the site.

**References**

**1)** Cortis, K., Micallef, K., and Mizzi, A. (2011). Imaging Paget's disease of bone-from head to toe. *Clinical Radiology*. Vol:66. 662-672. **2)** Vallet, M., and Ralston, S.H. (2016). Biology and Treatment of Paget's Disease of Bone. *Journal of Celluar Biochemistry*. Vol:117. 289-299. **3)** Barker, D.J.P., Chamberlain, A.T., Guyer, P.B., Gardiner M.J. (1980). Paget's disease of the bone: The Lancashire focus. *British Medical Journal*. Vol:280. 1105-1107. **4)** Van Staa, T.P., Selby, P., Leufkens, H.G.M., Lyles, K., Sprafka, J.M., and Cooper, C. (2002). Incidence and Natural History of Paget's Disease of Bone in England and Wales. *Journal of Bone and Mineral Research*. Vol:17. 465-471. **5)** Menéndez-Bueyes, L.R., and Fernández, M.D.C.S. (2017). Paget's Disease of Bone: Approach to Its Historical Origins. *Reumatología Clínica* (English Edition). Vol:13. 66-72. **6)** Gennari, I., DiSrefano, M., Merlotti, D., Gjordano, N., Martini, G., Tamone, C., et al. (2005). Prevalence of Paget's disease of bone in Italy. *Journal of Bone and Mineral Research*. Vol:20. 1356-64. **7)** Reasbeck, J.C., Goulding, A., Campbell, D.R., Beale, L.R., and Stewart, R.D.H. (1983) Radiological prevalence of Paget's disease in Dunedin, New Zealand. *British Medical Journal*. Vol:286. 1937. **8)** Detheridge, F.M., Guyer, P.B., and Barker, D.J.P. (1982). European distribution of Paget's Disease of Bone. *British Medical Journal*. Vol:235. 1005-1008. **9)** Boyleston, A., Ogden, A. (2005). A study of Paget's disease at Norton Priory, Cheshire. A medieval religious house. In: *Proceedings of the 5th annual conference of the British Association for biological anthropology and osteoarchaeology. BAR International Series. Archaeopress, Oxford*. Vol:1383. 69-76. **10)** Burrell, C.L., Gonzalez, S., Smith, L., and Irish, J.D. (2018) A Paget's-like disorder: Re-examination of Six Medieval Skeletons from Norton Priory, Cheshire, United Kingdom. *International Journal of Paleopathology*. **11)** Burrell., C.L. (2018) Skeletal Variation as a Possible Reflection of Relatedness within Three Medieval British Populations. *Unpublished Doctoral Thesis*. Liverpool John Moores University, UK. **12)** Valenzuluela, E.N., and Pietschmann, P. (2017). Epidemiology and pathology of Paget's disease of bone – a review. *Wiener Medizinische Wochenschrift*. Vol:167. 1-2, 2-8. **13)** Schmidt-Schultz *et al*. 2004. **14)** DeWitte, S.N., Boulware, J.C., and Redfern, R.C. (2013). Medieval monastic mortality: hazard analysis of mortality differences between monastic and nonmonastic cemeteries in England. *American Journal of Physical Anthropology*. Vol:152. 322-332. **15)** Müldner, G., and Richards, M.P. (2007). Diet and diversity at later medieval Fishergate: the isotopic evidence. *American Journal of Physical Anthropology*. Vol:134. 162-174. **16)** Guyer, P.B. (1981). Paget's disease of bone: The anatomical distribution. *Metabolic Bone Disease and Related Research*. Vol:4. 239-242. **17)** Winn, N., Lalam, R., and Cassar-Pullicino, V. (2016). Imaging of Paget's disease of bone. *Wiener Medizinische Wochenschrift*. Vol:167. 1-9. **18)** Rogers, J., Jeffrey, D.R., and Watt, I. (2002). Paget's disease in an archaeological population. *Journal of Bone and Mineral Research*. Vol:17. 1127-1134. **19)** Aykroyd, R.G., Lucy, D.A., Pollard, M., and Roberts, C.A. (1999). Nasty, Brutish, but Not Necessarily Short: A Reconsideration of the Statistical Methods Used to Calculate Age at Death from Adult Human Skeletal and Dental Age Indicators. *American Antiquity*. Vol;64. 55-70.

**Acknowledgements**

Funding was provided by the Doreen Beck Student Research Bursary, a grant from the Paget's Association who have provided extensive interest and support in this project and its development. The authors would like to dedicate this paper to the late Doreen Beck. Doreen has raised funds that have been used for many research projects over the years. Her tireless fundraising efforts have benefited Paget's research immensely. You will always be remembered for your generous support..

The authors would like to thank the Frank Hargrave and the Norton Priory Trust for their continuous support of our research. We would like to individually thank, Diana Wilkinson from the Paget's Association; Dr Darrell Green and Prof William Fraser from the University of East Anglia; Dr. Anna Daroszewska and Professor Robert Van 't Hof at the University of Liverpool for their expertise, discussions and support during this research.