

New Genes for Paget's disease

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Paget's disease disrupts the body's normal process of breaking down old bone and replacing it. It leads to enlarged bones with an abnormal structure and patients can suffer from bone pain, brittle bones that are susceptible to fractures, and arthritis. It affects more people in the UK than anywhere else in the world.

Genetic factors are important for the development of Paget's disease but until now only one gene was known to cause the disease. This gene, SQSTM1 is found in 10% of patients with the condition but until recently, the other genes remained unidentified.

In a study recently published in the journal Nature Genetics, we identified three new genes that strongly predispose to Paget's disease. These genes were discovered using the technique of genome wide association (GWAS); a powerful tool available to researchers for the past 3-4 years. It allowed us to test over 300,000 genetic variations that cover the entire human genome and examine their association with Paget's disease in a large group of 1250 affected patients and 1500 healthy individuals. Many of these patients were from the UK, but it also involved multinational collaboration with researchers from Australia, New Zealand, Spain and Italy. It included samples from many patients, who took part in the PRISM study, which many readers of the newsletter will be familiar with.

The study showed that variations in three genes were strongly associated with the risk of developing Paget's disease (PDB risk). The association was so strong that when combined, the variations in these genes appeared to contribute to 70% of PDB risk. RANK and M-CSF are two of the identified genes which are already known to be involved in regulating the rate of bone turnover thus providing an explanation why Paget's disease might occur. Optineurin, the third gene, had not previously been implicated in the process of bone turnover but these new findings suggest that it probably plays an important role in this process and in the development of Paget's disease.

Identifying these new genes represents an important advance in understanding why Paget's occurs. As the strength of association is so high this suggests that it may be possible to develop a screening test to identify people at high risk of developing the condition with the possibility of giving treatment at an early stage before damage to the bones has occurred

Although this is an important discovery, further research is needed to determine exactly why these gene variations predispose to Paget's disease.

We also want to extend our research since our studies showed that an additional three genes might also contribute to the development of the disease and we would hope to confirm this by studying additional patients. Another aim of our future research is to determine if gene testing could identify those patients who develop complications associated with Paget's disease such as fractures, arthritis, bone deformity and their response to treatment. We hope to be able to do this by looking at these new gene variants in the PRISM study where detailed information on disease complications and treatment response was recorded.

Readers of the newsletter will be familiar with the ZIPP study in which we are testing people with a positive family history of Paget's for a change in the SQSTM1 gene and conducting a clinical trial to determine if Zoledronic acid treatment can delay or prevent the onset of the disease. It is currently unclear whether these new variants carry the same risk of developing Paget's disease as SQSTM1 gene changes but this is an area that our research is focussing on at this present time.

If you have a family history of Paget's and are interested in taking part in our research please contact the ZIPP trial office in Edinburgh on 0131-537-3851 or by emailing zipp@ed.ac.uk