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Bone disease traced to the Middle Ages

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The special form of the bone disease osteopetrosis that exists in Västerbotten is due to a gene mutation that can be traced back to the Middle Ages and leads to defective bone resorption, according to new research led at Uppsala University.

A healthy skeleton has a balance between the new formation and breakdown of bone tissue, which keeps the amount of bone mass constant. Bone is formed by a cell type called osteoblasts, while osteoclasts from bone marrow facilitate the resorption process.

With osteopetrosis, or marble bone disease as it used to be called, the ability to break down bones is absent. Because bone formation is normal, bone mass gradually increases, space for bone marrow contracts, and blood formation is disturbed. This leads to anemia and greater susceptibility to infection. Despite substantial bone mass, the skeleton becomes brittle and prone to fractures. The channels in the skull through which the hearing and optic nerves run are blocked by bone and patients often become blind and experience hearing loss.

Osteopetrosis is a very rare hereditary disease. It is known to occur in Västerbotten and has thus been named the Västerbotten form of osteopetrosis. There are currently five known patients with the disease, one of whom underwent a bone marrow transplant and has become healthy.

A research team led by Eva-Lena Stattin, researcher at the Department of Immunology, Genetics and Pathology at Uppsala University and

senior physician at Uppsala University Hospital; Ulf Lerner, senior professor at the Centre for Bone and Arthritis Research at Gothenburg University; and Petra Henning, researcher at Sahlgrenska Academy, have now shown that patients in Västerbotten have a common origin, that the disease is due to a mutation in the gene that codes for the protein sorting nexin 10 (SNX10), and that the mutation occurred 950 years ago.

The Västerbotten form is a form of hereditary osteopetrosis (IOP). The study has shown that the disease has a clear debut with symptoms already at birth. Even though the SNX10 gene is not only expressed in osteoclasts, but also in other cells, a comprehensive clinical mapping has shown that the mutation that Västerbotten patients have only affects the skeleton. In addition to fractures, increased susceptibility to infection, vision and hearing problems, the mutation also leads to impaired tooth development and, above all, to delayed tooth eruption.

With the help of cells isolated from patients' blood and extensive cell and molecular biological techniques, together with microscopy and electron microscopy, the research group has shown that the mutation does not affect the formation of osteoclasts, but that these cells have completely lost the ability to break down bone. This is due to a defective specialised structure called the "ruffled border", which is essential for the cells to be able to dissolve the mineral and break down the proteins in bones. Further studies will explain how SNX10 influences the formation of the ruffled border.

Because osteoclasts are from bone marrow cells, this form of osteopetrosis can now be cured with bone marrow transplants.

More information: Eva-Lena Stattin et al. SNX10 gene mutation leading to osteopetrosis with dysfunctional osteoclasts, *Scientific Reports* (2017). DOI: 10.1038/s41598-017-02533-2

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