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BONE

Role for *PLS3* in X-linked osteoporosis revealed

A new study from a Dutch team has shown that *PLS3*, which encodes plastin 3 (an actin-bundling protein) is involved in X-linked osteoporosis.

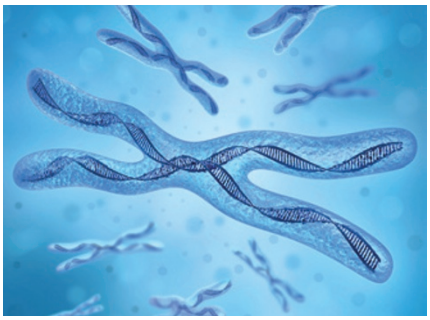
The identification of a family with X-linked inheritance of osteogenesis imperfecta or osteoporosis with fractures prompted the research team to conduct a broader study of the genetics underlying osteoporosis. Linkage analysis was undertaken in two families, and targeted next-generation sequencing was carried out in three affected male patients from one of the families to sequence all the exons on the X chromosome.

"Our approach led to the identification of a frameshift mutation in a very unlikely candidate gene, *PLS3*, that is expressed in nearly all tissues and was already known to be a protective modifier in spinal muscular dystrophy," explains corresponding author Gerard Pals (VU University Medical Center, Netherlands). Further analysis using Sanger sequencing of the *PLS3* exons in 95 unrelated affected men identified a further four families with disruptive mutations in this gene.

Analysis of zebrafish and of fibroblasts cultured from patients found that plastin 3 is involved in bone formation and remodelling, and possibly mechanosensing. For example, knockdown of *pls3* in zebrafish resulted in malformations in the development of the craniofacial bone structure, body axis and tail. These malformations could be reversed with the administration of human *PLS3* mRNA.

In addition, an analysis of participants from the Rotterdam Study showed that a variant of *PLS3* seems to be involved in osteoporosis in elderly women from the general population. The variant was associated with reduced BMD and increased incidence of fracture. "The relative risk of 1.95 is the highest recorded so far for osteoporosis," notes Pals. However, the association with fracture risk was not fully explained by BMD, and was not found in elderly male participants, which suggests that other factors might be involved in osteoporosis and fractures in this population.

These findings suggest that the formation of actin bundles in osteocytes, which requires plastin 3, is an important and previously unknown factor in bone formation and remodelling. Plastin 3 could therefore be an important diagnostic tool for young male patients with unexplained fractures and osteoporosis.



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The research team are currently performing experiments to further explain the involvement of actin bundling in bone remodelling and disease. The team suggests that mutations in *PLS3* lead to decreased mechanosensing of osteocytes, which dysregulates bone modelling or remodelling, resulting in osteoporosis and fractures. They are also studying mutations and variants in *PLS3* in women with unexplained osteoporosis and/or fractures. "In the future, we aim to develop therapies based on our findings," says Pals.

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Original article van Dijk, F. S. *et al. PLS3* mutations in X-linked osteoporosis with fractures. *N. Engl. J. Med.* doi:10.1056/NEJMoa1308223