Introduction
Mutations in the gene PLS3 have recently been found as being a cause of early-onset primary osteoporosis. This type of osteoporosis affects males more often and more severely than females, because PLS3 is located on the X-chromosome. Clinically patients with PLS3 mutations present similarly to patients with defects in collagen type I, Osteogenesis Imperfecta (OI), and some suggest that patients with PLS3 mutations should be classified as having OI type 4 (common variable OI).

However, PLS3 is not involved in the processing of type I collagen. One suggestion has been that PLS3 is involved in the mechanosensitivity of the osteocytes. Another suggestion has been that PLS3 modulates the onset of the mineralization process in bone.

Aim
The aim of this study was to explore the question of how prevalent PLS3 mutations are in childhood-onset primary osteoporosis, as not all patients with childhood-onset primary osteoporosis get a molecular diagnosis.

Methods
Using PCR and Sanger sequencing techniques, all coding exons and exon-intron boundaries of the PLS3 gene were sequenced for all the included 32 patients. In one Finnish male patient, RNA was extracted from fibroblasts using Trizol Reagent, and cDNA was later made using RT-PCR.

Patients
In this study, thirty-two (32) patients with childhood-onset primary osteoporosis, without a molecular diagnosis, were included.

The diagnosis of primary osteoporosis was based on:
- Exclusion of secondary osteoporosis.
- Low BMD with a history of recurrent, low impact, peripheral fractures and/or vertebral compression fractures.

Clinical information about the patients

Results
In a 28-year-old Finnish male we found a previously not described stop-gain mutation (c.766C>T; p.Arg256X). This male patient has a history of multiple vertebral compression fractures since early childhood and a markedly low BMD. He also has slightly blue sclerae and joint hyperlaxity. The PLS3 mutation was inherited from his mother, who is heterozygote for the mutation, and has a milder phenotype with osteopenia and joint hyperlaxity.

In the remaining thirty-one (31) patients we found several variants in PLS3, but none of these variants were regarded as disease-causing.

Conclusions
PLS3 mutations explain some cases of early-onset osteoporosis. Our results do not support first-line screening of PLS3 in patients with childhood-onset primary osteoporosis. However, we would recommend PLS3 screening - especially in males - if COL1A1 and COL1A2 screening is negative.

PLS3 gene variation in childhood fractures and primary osteoporosis
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