Introduction
Early-onset osteoporosis presents as bone weakness and increased risk of fractures in children and young adults. The genetic causes and molecular mechanisms underlying this disease are poorly defined. However, the study of other rare bone diseases has recently led to the identification of new genes causing osteoporosis.

Aim of the project
To explore the role of variations in the cartilage-associated protein (CRTAP) gene in early-onset osteoporosis and/or recurrent fractures.

Patients
1) Eleven-year-old Iraqi girl with severe osteogenesis imperfecta (OI) (Fig. 1)
2) Osteoporosis group (30 patients). Inclusion criteria:
   • a BMD Z-score below -2.0 and/or
   • a history of increased bone fragility (at least three peripheral fractures and/or one or more vertebral compression fractures)
   • exclusion of secondary osteoporosis and
   • age below 30 years before the diagnosis of osteoporosis
3) Fracture-prone group (66 patients). Inclusion criteria:
   • age between 4-16 years
   • a history of at least two low-energy long bone fractures before age 10 years, three low-energy long bone fractures before age 16 years, and/or at least one low-energy vertebral compression fracture

Methods
- Homozygosity mapping with 1-2 STS-markers
- Sanger sequencing

Results

Index girl with OI
- Novel one-nucleotide frameshift duplication c.141dupC (p.Tyr48Leufs*113) (Fig. 2)

Osteoporosis group and fracture-prone group
- 5 synonymous single nucleotide polymorphisms (SNPs) (Table 1)

Table 1 Genetic variants identified in the CRTAP gene. The minor allele frequencies (MAFs) were comparable to healthy population (p>0.05)

Conclusions
- We identified a novel CRTAP homozygous mutation, c.141dupC, in a girl with severe OI (Fig. 3)
- We confirmed absence of carrier phenotype in her parents
- We excluded monoallelic variants in CRTAP as common risk factors for milder skeletal fragility

Fig. 2 Pedigree of the family and Sanger electropherograms of the frameshift mutation c.141dupC (p.Tyr48Leufs*113).

Fig. 3 A schematic representation of the CRTAP gene and location of all exonic and intronic pathogenic variants that have previously been reported in literature, marked on left side of the diagram. All the genetic variants found in our study, the c.141dupC and the 5 SNPs, are marked on the right side of the figure.