Introduction
Disproportional short stature (DSS) is the most frequent clinical presentation of skeletal dysplasias, which are a heterogeneous group of more than 450 disorders of bone. Skeletal survey is important to establish the diagnosis and to guide the genetic test, but it has several limitations, especially in mild and atypical cases.

Objectives
To identify the genetic aetiology of disproportional short stature by exome sequencing (WES).

Methods
DNA
Library Prep
WES
FASTQ
VCF
Sanger

6 patients and available relatives n= affected n= unaffected

Our analysis focused on functional variants absent in controls (ExAC, ESP6500, 1000Genomes and 1,216 alleles from healthy ethnic matched individuals) that segregate in the families.

Results
The mean coverage of the captured regions was 170x (99.6% of target region with more than 10x). Each patient had an average of 64,490 allele variants. All pedigrees suggested an autosomal dominant pattern of inheritance.

We identified a causative variant predicted as pathogenic in 3 patients:
- Case 1 with height SDS of -2.0 has a novel heterozygous mutation in NRP2 gene (c.2905G>C, p.Val969Leu) (Figure 1 and Table 1). Heterozygous mutations in NRP2 are a cause of short stature without a distinct phenotype.

- Case 2 with height SDS of -4.5 has a heterozygous mutation in FBNI gene (c.5183C>T, Ala1728Val) (Figure 2 and Table 2). Mutations in FBNI were associated with gelesphyic and acromic dysplasias, but this patient lacks some of the cardinal features of these conditions.

- Case 3 with height SDS of -2.5 and bilateral osteonecrosis of the femoral epiphysis has a heterozygous mutation in COL2A1 gene (c.1652G>A, p.Gly571Ser) (Figure 3 and Table 3). Mutations in COL2A1 cause several skeletal disorders with highly variable phenotype.

Conclusions
We identified 3 heterozygous mutations in 3 different genes that explain the disproportional short stature phenotype observed in our patients. Because of the mild and unspecified phenotype, only a genomic approach allowed the identification of the aetiology of short stature in these patients.

References