rs72658163, a new heterozygous variant in COL1A2 associated with atypical femoral fracture

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Introduction

Atypical femoral fractures (AFF) of the subtrochanteric region are rare. Bisphosphonates account to a large extent to their occurrence, however AFF also occur without exposure to bone medication. Some observations of patients with bone genetic disorders (like hypophosphatasia, HPP) who encountered AFF have suggested a possible genetic predisposition to this rare event.

We here assessed the genetic factors associated with AFF among subtrochanteric fractures.

Methods

Data sources and classification criteria

- 3 French academic hospitals in Paris, Poitiers and Amiens
- identified using ICD-10 codes for subtrochanteric fractures (S72.2) or for femoral shaft (S72.3) in patients > 50 years-old.
- files including medical records and admission standard radiographs of the entire femur were reviewed by 2 rheumatologists
- excluded in case of high-trauma, if associated to a pathological condition such as bone metastasis or were periprosthetic, when fractures were not subtrochanteric or in the femoral shaft (miscoding), and when medical information was missing
- classified as typical or atypical according to the ASBMR 2014 Task Force

Results

1. Flow chart

2. Patient’s characteristics

3. Genetic analysis

4. rs72658163

Variant of COL1A2

- Variation of unknown significance
- Missense variant
dDNA level: NM_000089.3:c.2123G>A
gDNA level: Chr7(GRCh37)g.94049588G>A
protein level: p.Arg708Gln
protein change R618Q
- Described in a lethal form of Osteogenesis imperfecta [1], in an atypical form of Marfan Syndrome [2]
- Causes abnormal proα2(I)collagen in type I collagen fibrillogenesis in vitro [3]
- Allele Frequency ExAC= 0.07% (All) 0.08% (Eur)
- PolyPhen-2 = Potential damaging score = 1

Conclusion

- AFF is a rare event.
- AFF can occur with (36%) or without (64%) bisphosphonate exposure
- Out of the 5 analyzed patients, we found 1 variant of COL1A2 that might be associated with bone matrix abnormality, and 3 common variants in TNFSF11
- Further NGS screening in AFF is needed to confirm a genetic predisposition

References