P415

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

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Introduction

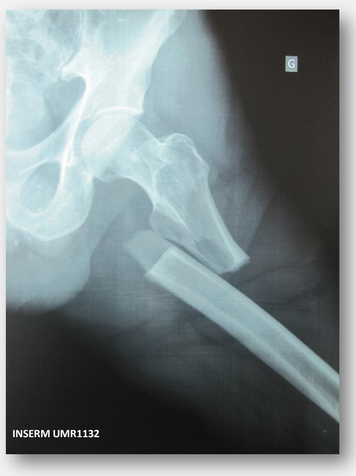
Atypical femoral fractures (AFF) of the subtrochanteric region are rare. Bisphosphonates account to a large extent to their occurrence, however AFF also occur without exposure to bone medication.

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.

Objective

To determine the genetic variants for TNSALP or COL1A1/COL1A2 genes in patients with AFF



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 when they 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**

Genetic assessment

- Patients with AFF were called and asked to participate to the genetic evaluation.
- After informed consent, blood was drawn for genetic tests.
- The array included following genes for HPP diagnosis and differential diagnosis: *ALPL*, *COL1A1*, *COL1A2*
- Next generation sequencing (NGS) : Ion Torrent Personal Genome Machine (PGM)
- Confirmation of mutations by the Sanger method

Results

1. Flow chart

389 women and men (≥ 50 yrs), DP S72.2 and S72.3, without DA cancer, between 2007 and 2010

- **179 had fractures on prosthesis or other material**
- **25 had traumatic fractures**
- **17 had pathological fractures**
- **30 had per-troch fractures**
- **17 had no medical information**

ST/FS Fractures n = 121

- **Typical n = 107**
- **Atypical n = 14**

2. Patient's characteristics

	Atypical fractures n=14	Typical fractures n=107	p-value
Demography			
Age (yrs)	73±10	79±11	0.08
Weight (kg)	64±17	66±16	0.42
Height (cm)	158±13	163±9	0.15
BMI (kg/m²)	27±5	26±5	0.43
Female (%)	12 (86%)	78 (73%)	0.52[a]
Associated diseases and bone treatments (number and %)			
HTA	8 (62%)	73 (70%)	0.54[a]
Diabetes	1 (8%)	18 (17%)	0.69[a]
Cognitive Function	5 (38%)	50 (48%)	0.51
Arrhythmia	1 (8%)	24 (23%)	0.29[a]
Lipid disorders	4 (31%)	29 (28%)	0.76[a]
Calcium /vitamin D supplements	5 (38%)	9 (9%)	$<10^{-2}$ [a]
Bone treatment	5 (36%)	5 (5%)	$<10^{-2}$ [a]

[a]: Fisher's exact test

3. Genetic analysis

Patient	Age	Traitement for OP	TNSALP	COL1A1/A2
1	75	Raloxifene	ND	ND
2	74	Alendronate	NONE	ND
3	76	Alendronate	ND	ND
4	65	Alendronate	ND	ND
5	78	Risedronate	Heterozygous polymorphism c.1365C>T (p.Gly455Gly)	**Heterozygous polymorphism c.2123G>A (p.Arg708Gln) on COL1A2**
6	87	None	Heterozygous polymorphism c.1542G>T (p.Ala514Ala)	NONE
7	69	None	ND	ND
8	80	None	ND	ND
9	54	None	Heterozygous polymorphism c.787T>C (p.Tyr263His), c.862 20G>T, c.862 51G>A, c.863-7T>C, C.863-12C>G, c.876A>G (p.Pro292Pro)	ND
10	85	None	ND	ND
11	83	None	ND	ND
12	77	None	NONE	NONE
13	61	None	ND	ND
14	61	None	ND	ND

4. rs72658163

Variant of COL1A2

- Variation of unknown significance
- Missense variant
- cDNA 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], an in an atypical form of Marphan Syndrom [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 TNSALP**
- **Further NGS screening in AFF is needed to confirm a genetic predisposition**

[1] Forlino A, Keene DR, Schmidt K, Marini JC. An α2 (I) glycine to aspartate substitution is responsible for the presence of a kink in type I collagen in a lethal case of osteogenesis imperfecta. Matrix Biol. 1998;17(8):575–584.

[2] Phillips CL, Shrago-Howe AW, Pinnell SR, Wenstrup RJ. A substitution at a non-glycine position in the triple-helical domain of pro alpha 2(I) collagen chains present in an individual with a variant of the Marfan syndrome. J Clin Invest. 1 nov 1990;86(5):1723‑8.

[3] Vomund AN, Braddock SR, Krause GF, Phillips CL. Potential modifier role of the R618Q variant of proα2(I)collagen in type I collagen fibrillogenesis: in vitro assembly analysis. Mol Genet Metab. juin 2004;82(2):144‑53.