Rare Causes of Osteogenesis Imperfecta are Common in Consanguineous Pedigrees

P1-175

Sare Betul Kaygusuz[1], Ahmet Arman[2], Saygin Abali[3], Pınar Ata[2], Tarık Kırkgoz[1], Mehmet Eltan[1], Zehra Abali[1], Didem Helvacioglu[1], Busra Tosun[1], Tuba Menevse[1], Tulay Guran[1], Abdullah Bereket[1], Serap Turan[1]

[1]Marmara University, Department of Pediatrics, Division of Pediatric Endocrinology, Istanbul, Turkey
[2]Marmara University, Department of Medical Genetics, Istanbul, Turkey
[3]Acibadem University, Department of Pediatrics, Division of Pediatric

Background

- **Osteogenesis imperfecta (OI) :**
  - Low bone mass and bone fragility
  - Mainly due to *COL1A1*/*COL1A2* gene defects.
  - >17 genes have been identified in the pathogenesis
- **Aim:** Characterize genotypic spectrum of our OI cohort.

Methods

- **47** OI patients (28 males)
- **38** different families (13 consanguineous/9 multiplex)
- Screened with the next-generation sequencing (NGS) panel for 15 OI genes
- Sanger sequencing was used for confirmation and segregation analyses
- Sillence classification was used to define clinical severity

Results

- ***COL1A1:*** **19** patients (**15** families): 14 different mutation, 4 novel
- ***COL1A2:*** **3** patients (**3** families): 3 different mutations
- ***FKBP10:*** **9** patients (**6** families):
  - **4** patients (**2** families) also had Epidermolysis Bullosa
    - Founder mutations: *FKBP10* (p.Met107_Leu117del) /*KRT14* (p.Tyr204*)
  - **4** patients (**4** families) had 3 novel *FKBP10* mutations
  - **2** Siblings (**1** OI-III and **1** BS): p.Ser8Glnfs*67
- ***SPARC:*** **2** patients (**1** family)*:* Novel homozygous mutation
- ***P3H1:*** **3** patients (**3** families)**:** Novel homozygous mutation
  - Typical features of round face and long fingers.
- ***IFITM5:*** **1** patient; paternally inherited heterozygous
- ***WNT1:*** **1** patient with congenital ptosis
- ***CRTAP:*** **1** patient*:* Novel homozygous
- ***BMP1:*** **2** patients (**1** Family)

Table 1: Mutation analysis and phenotypic characteristics of patients

Sillence Type	Gene	N individuals (M/F)	Blue Sclera (+)	Dentinogenesis Imperfecta(+)
OI-I	*COL1A1* p.Gly260Asp **p.Gly329Val** p.Gly560Ser p.Gln202Ter **p.Ala714Profs*6** p.Ala1256Profs*75 **IVS2 +1G>A** IVS5+1G>A IVS17+1G>C	12(6/6)	12	6
	COL1A2 p.Gly601Ser, IVS15-2A>G	2 (2/0)	2	2
	Unknown	1(1/0)	1	0
OI-II	*COL1A1* p.Gly704Ser	1(1/0)	1	NE
OI-III	*FKBP10* p.Met107_Leu117del **p.Gly300Ter** **p.Leu105_Arg115del** p.Ser8Glnfs*67	8 (5/3)	4	2
	COL1A1 p.Gly1076Ser **p.Gly413Leufs*122**	2 (0/2)	2	NE
	SPARC **p.Glu54Ter**	2 (1/1)	2	0
	P3H1 **p.Met206Ile, c.941-1G>A**	2 (1/1)	3	2
	COL1A2 p.Gly773Ser	1(1/0)	1	1
	WNT1 p.His267Profs*30	1(1/0)	1	1
	LRP5	1(1/0)	*pseudoglioma	1
	SERPINF1 **p.Ile301Argfs*21**	1(1/0)	0	1
OI-IV	*COL1A1* p.Gly218Asp, p.Arg598Ter	4 (0/4)	4	3
	CRTAP **p.Glu179Ter**	1(1/0)	1	1
	BMP1 **p.Arg371His**	2(2/0)	0	0
	P3H1 **p.Leu149Arg**	1(0/1)	1	0
	Unkonwn	3(3/0)	3	1
OI-V	*IFITM5* c.-14C > T	1(0/1)	1	1
Bruck Syndrome Type 1	*FKBP10* p.Ser8Glnfs*67	1(1/0)	1	1

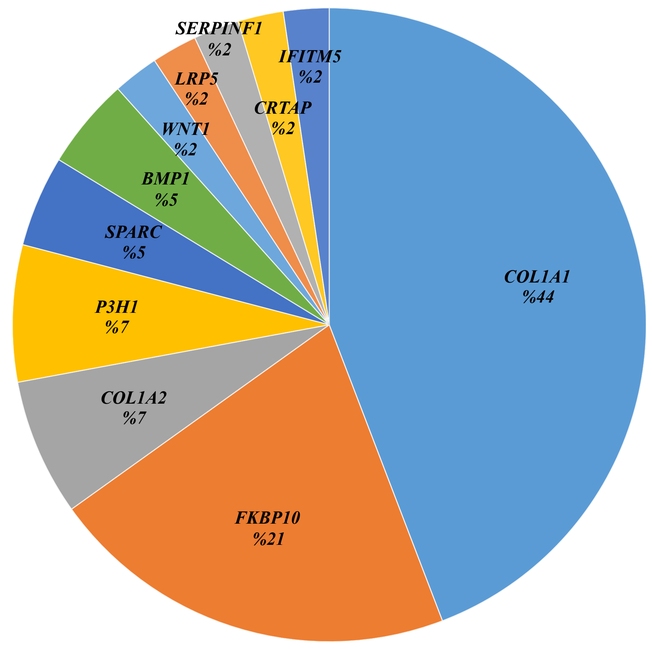

Figure 1: Mutation analysis of patients

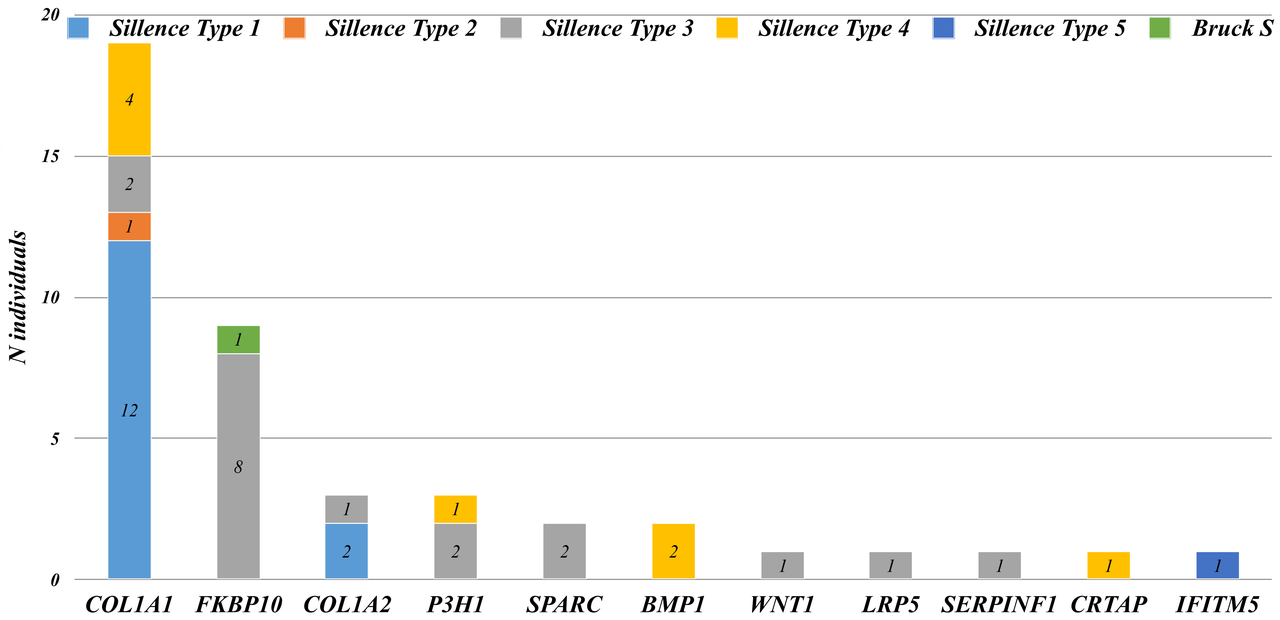

Figure 2: Relationship between clinical sillence types and gene mutations

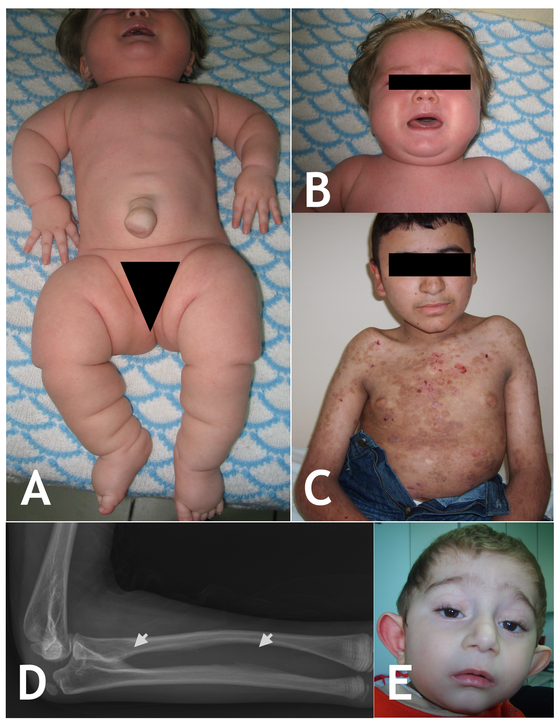

Figure 3: Phenotypic characteristics of patients:
A, B- Patient with LEPRE mutation with round face,short barrel shaped chest, shortening of the long bones.
C- Patient with co-segregated FKBP10 and KRT14 with epidermolysis bullosa.
D- Forearm radiograph of patient with IFITM5 mutation showing calcification of the interosseous membrane between the radius and ulna (white arrow).
E- Patient with congenital bilateral ptosis had WNT1 mutation.

Conclusions

- We were able to identify the molecular etiology in 79% of our OI cohort by NGS panel.
- We detected 15 novel mutations in 7 different genes.
- 49% of the defects were in non- *COL1A1*/*COL1A2* genes and 80% of them coming from consanguineous families.
- Although *COL1A1* and *COL1A2* gene defects were the most common molecular etiologies,we have identified relatively higher frequencies of rare genetic causes of OI in our cohort.
- Rare causes of OI should be considered particularly in cases with consanguineous parents and/or with associated abnormalities.