Frequency of Recessive Osteogenesis Imperfecta in a Turkish Cohort and Genetic Causes

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Background

Osteogenesis imperfecta(OI) is a heterogeneous group of brittle bone disease mostly caused by quantative or qualitative defects in type I collagen. In most populations, more than 90% of the patients with OI have dominant mutations in *COL1A1* or *COL1A2* genes (AD-OI). Less than 10% of the cases have recessive inheritance (AR-OI). Currently 12 genes have been identified as a cause of AR-OI.

Objective and hypotheses

We assumed higher frequency of AR-OI in our population because of high consanguineous marriages and aimed to detect AR-OI rate and distribution of genetic causes in our cohort.

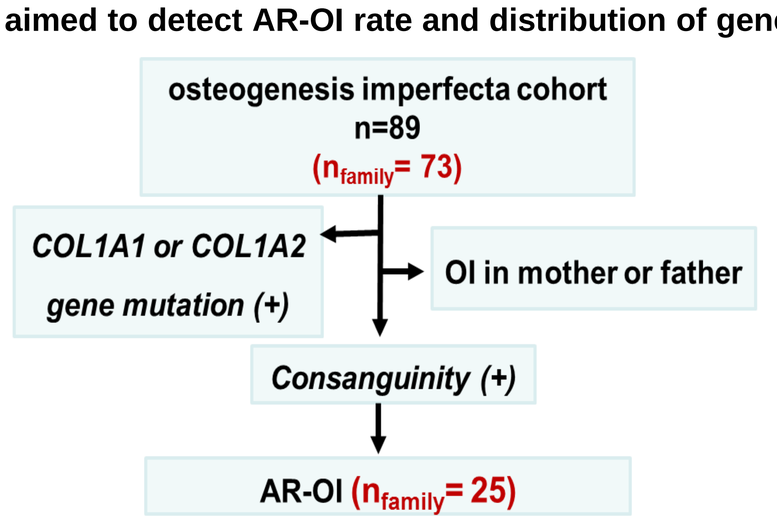
Method

Eighty-nine patients from 73 families were evaluated for inclusion.

The patients having parental OI history (27 families) and/or

patients with mutations in COL1A genes (5 families) were accepted as AD-OI.

The patients born to consanguineous parents were included as AR-OI (29 patients/25 families).



In AR-OI group;

Two patients had osteoporosis-pseudoglioma and

Five patients (4 families) had epidermolysis bullosa and found to have founder mutation of p.delGly107_Leu117del in *FKBP10* gene.

Remaining 19 families were called for genetic analyses.

Three patients were died.

Whole exome sequencing (WES) was performed to 7 index patients.

Results

Novel mutations in *LEPRE1*, *CRTAP* and *FKBP10* genes were detected in WES (Table).

We also detected a nonsense mutation in *SPARC* in two siblings which is a newly described AR-OI gene (P1-P109)

Two cousins with severe platyspondily had mutation in *BMP1* gene.

The other two index cases are still under investigation.

Genetic etiology in our AR-OI cohort

Genotype	n (family)	N (patient)
FKBP10	5	7
LRP5	2	2
LEPRE1	1	1
CRTAP	1	1
SPARC	1	2
BMP1	1	2
Not known yet	10	11
Exitus	3	3
Total	25	29

Overall, the frequency of recessive OI was 34.2% of the families and 32.6% of the patients.

Table. Clinical and genetic features of patients having different mutations detected with WES

	P1	P2	P3.1	P3.2	P4.1	P4.2	P5.1	P5.2
Gene	LEPRE	CRTAP	FKBP10		SPARC		BMP1	
Mutation	c.618G>A Splice site mutation in Exon 2	c.535G>T p.Glu179X	15-16insC p.4Gly_5Profs		c.160G>T p.Glu54X		c.1112G>A p.Arg371His	
Sillence OI Type	3	3	3	3	4	4	4	4
Age at diagnosis (month)	0.5	0.3	6.0	0.1	3.0	0.5	4.8	12.6
Antenatal sign	ND	Short femur	ND	ND	ND	ND	ND	ND
Gestational week and delivery	28 GW, C/S	35 GW, Breech C/S	40 GW, VD	35 GW, Breech; C/S	40 GW, VD	40 GW, C/S	38 GW, C/S	40 GW C/S
Birth weight (g)	2000	2240	2800	2800	2500	2900	2750	3400
Extremity deformity	+	+	+	+	+		-	-
Vertebral deformity	-	-	+	+	+	+	+	+
Rib fracture / Thorax deformity	+/-	+/+	+/+	NA/-	NA/-	-/-	-/-	-/-
Joint laxity	+	-	-	-	+	+	-	-
Blue / grey sclerae	-	+	+	+	+	+	-	-
Dentinogenesis imperfecta	+	NA	-	NA	-	NA	-	-
Umblical hernia / inguinal herni	+/-	+/+	-/-	+/-	-/+	-/-	-/-	-/-
Nefrolithiasis	-	+	-	-	-	-	-	-

Conclusion

✓ In our cohort of OI, 1/3 of patients have AR-OI. In 11 families with genetic results, five *FKBP10,* two *LRP5*, and one each *LEPRE1, CRTAP, BMP1* and *SPARC* gene mutation have been detected.

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