Targeted Molecular Genetic Diagnosis by Next Generation Sequence Analysis Method and Investigation of Responsible Candidate Genes in Patients with Osteogenesis Imperfecta

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Introduction: Osteogenesis imperfecta (OI) is a rare single gene disorder characterized by osteoporosis, increased risk of bone fracture, bone deformities and short stature. About 17 genes responsible for OI have been identified to date. Mutations in the *COL1A1* and *COL1A2* genes encoding type 1 collagen account for approximately 70-80% of the etiology.

Objective: The aim of this study was to investigate the molecular genetic etiology and to determine the genotype-phenotype relationship with targeted next generation sequencing (NGS) in patients with OI phenotype.

Material and Methods: OI patients followed by Ege University Medicine Faculty Pediatric Endocrinology Department. 42 patient were included:

- Clinical typing (Sillence 1979)
- Demographic features
- Auxological measurements

All genes known to be responsible for OI and all genes known to play role in collagen / bone synthesis were studied by NGS-TrusightOne®

RESULTS

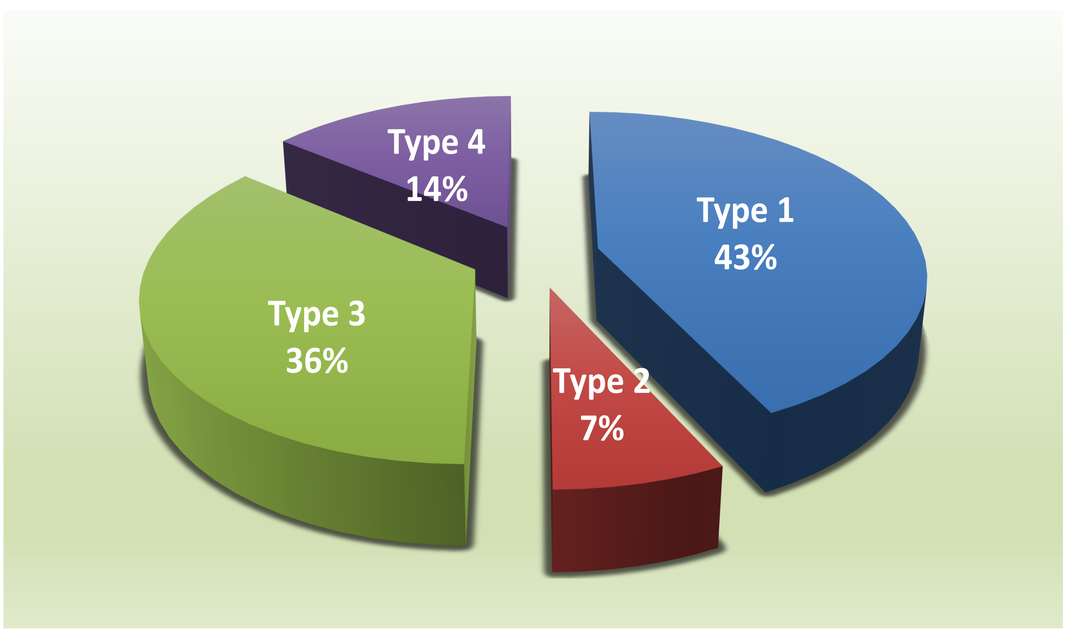

Figure 1: Distrubution of clinical typing

Consanguinity	13 (31%)
Family History	21 (50%)
Admission age	4.5 ± 3.8 years
Median body weight SDS (min-max)	-1.3 (-6.8-1.2)
Median height SDS (min-max)	-2 (-7.6-0.8)
Bone deformity	23 (54.8%)
Unaided mobiliation	22 (52.4%)
Blue sclera	27 (64.3%)
Scoliosis	11 (26.2%)
Dentinogenesis imperfecta	6 (14.3%)
Hearing loss	2 (4.8%)

Table 1: Clinical features of all patients (n:42)

COL1A1 and *COL1A2* genes mutation in 24 of 42 cases (+) (7 novel mutations)

18 cases without mutation

Targeted NGS Analysis

9 cases (6 novel mutations)

COL1A1 gene 20 cases (47.6%) | COL1A2 gene 3 cases (7.1%) | COL1A1+COL1A2 genes 1 case (2.3%)

SERPINF1 gene 4 cases (9.5%) | *P3H1* gene 1 case (2.3%) | *FKBP10* gene 4 cases (9.5%)

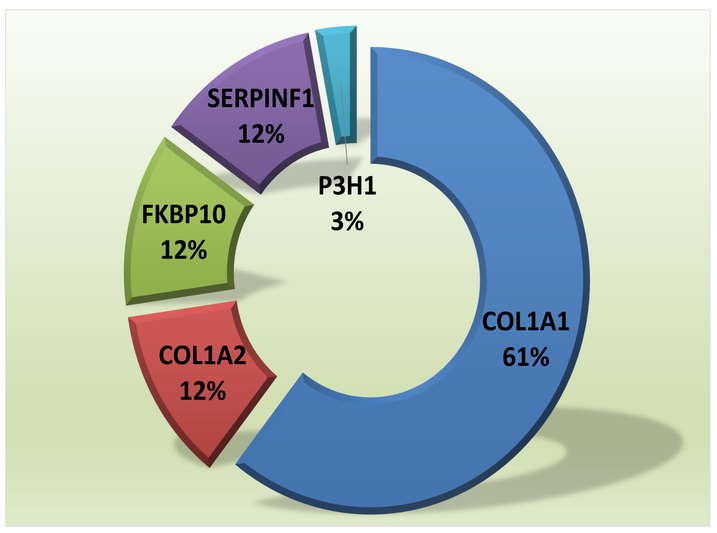

Figure 2: Distrubution of mutations (n:33)

	COL1A1 (n:20)	*COL1A2* (n:4)	*FKBP10* (n:4)	*SERPINF1* (n:4)	*P3H1* (n:1)
Gender	11 girl /10 boy	2 girl/2 boy	1 girl/ 3 boy	2 girl/2 boy	Girl
Admission age (years)	4.5 ± 3.8	2.05 ± 3.03	4.51 ± 3.22	5.76 ± 2	0.2
Consanguinity	2 (10%)	2 (50%)	(-)	2 (50 %)	(+)
Family history	10 (47 %)	2 (50%)	4 (100%)	2 (50 %)	(-)
Average height SDS	- 1.79 ± 1.52	-2.72 ± 0.87	3.06 ± 1.58	- 4.26 ± 2.30	2.12
Average weight SDS	-1.03 ± 1.10	- 3.35 ± 2.62	-2.14± 1.46	-2.86 ± 1.55	-0.36
Clinical Type	Type 1 : 10 (47.6 %) Type 2 : 2 (9.5 %) Type 3 : 7 (33.3%) Type 4: 2 (9.5 %)	Type 1 : 1 (25 %) Type 2 : 1 (25%) Type 3 : 1 (25%) Type 4: 1 (25 %)	Type 3 : 2 (50 %) Type 4 : 2 (50 %)	Type 1 : 2 (50 %) Type 3 : 2 (50 %)	Type 3

Table 2: Clinical features of patients with mutation (n:33)

Genetic etiology was determined in 33 (78.5%) of 42 cases by targeted sequence analysis

In our study,13 novel mutations in the OI genes were identified and made significant contributions to the literature

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Bone, growth plate and mineral metabolism

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