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Original Article

A Single-Center Retrospective Cohort Study of Genotype–Phenotype Correlation of Osteogenesis Imperfecta in UAE

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Abstract

Background Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous group of inherited connective tissue disorders characterized by skeletal fragility. Patients with OI suffer recurrent fractures, limb deformities, and kyphoscoliosis. Multiple extraskeletal manifestations might also be present. Autosomal dominant variants in the *COL1A1* or *COL1A2* genes account for approximately 90% of cases.

Objective The aim of the study was to describe the variant spectrum and genotype–phenotype correlations in patients with OI seen in Tawam Hospital in the UAE.

Methods The authors conducted a retrospective chart review for all patients with OI assessed by geneticists at Tawam Hospital from January 2010 to December 2021. They retrieved each patient's baseline characteristics, detailed history and physical examination, laboratory, imaging, and genetic results.

Results A total of 40 patients with OI were found and included in this study. The majority (80%) were Emirati, and 57.5% were females. Consanguinity was documented in 24.3%. Thirty-seven patients (92.5%) had positive molecular testing; 28 patients (75.7%) had an autosomal dominant inheritance, and 9 patients (24.3%) had an autosomal recessive inheritance. The majority had missense variants. Four variants were novel. A high prevalence of pathogenic variants in the *COL1A1* gene (57%) was found. Patients with variants in the *LEPRE1* gene had early and severe phenotypes, while patients with variants in the *TMEM38B* gene had variable presentations. The majority of patients (85%) had skeletal phenotypes: fractures, bone deformity, scoliosis, and

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- genotype–phenotype correlation
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osteopenia. Extraskeletal phenotypes included blue sclera, dentinogenesis imperfecta, hearing loss, and dysmorphic features.

Conclusion This study reports the genotype–phenotype correlation of OI patients from the UAE. A high prevalence of pathogenic variants in the *COL1A1* gene with OI type IV phenotype was found. Further multicenter more extensive studies are recommended.

Introduction

Osteogenesis imperfecta (OI) is a rare heterogeneous group of inherited connective tissue disorders characterized by skeletal fragility. Its frequency varies from 1:15,000 to 1:20,000.[1] Clinical features of OI are highly variable, ranging from stillbirth to lifelong absence of fractures. More severely affected patients with nonlethal OI suffer from recurrent limb fractures, limb deformities, vertebral compression fractures, and kyphoscoliosis.

Most OI cases are caused by an inherited defect affecting the production or modification of type 1 collagen, a major structural protein found in bones, teeth, ligaments, tendons, skin, sclera, and blood vessels. Besides the history of fragility fractures, patients with OI may also exhibit extraskeletal features such as blue or gray sclera, fragile skin, easy bruising, hernias, dentinogenesis imperfecta, joint laxity, short stature, deafness, and cardiac valve abnormalities.[2]

In 1979, Sillence et al classified OI into four types (types I, II, III, and IV) based on severity, phenotype, and radiological findings.[3] According to the modern classification, the disease is divided into five types. OI type V is caused by heterozygous variants in the interferon-induced transmembrane protein 5 (*IFITM5*) gene.[4] Patients with this form of OI tend to form a hyperplastic callus after fractures with a characteristic radiological feature of calcification of the interosseous membrane between the forearm bones. With the discovery of new causative variants, the Sillence classification has been expanded to OI type XXIII.[5]

Most OI forms (~90% of cases) are caused by autosomal dominant variants in *COL1A1* or *COL1A2* genes, which encode the polypeptide chains of type I collagen.[6] It is worth knowing that up to 25% of children have de novo OI in the absence of affected parents/family members. On the other hand, the variants in autosomal recessive genes are implicated in encoding proteins involved in the posttranslational modification, processing, transport, and cross-linking of collagen type I.[7] Generally, children with these variants tend to have moderate to severe forms of OI.

Nearly 20 new genes responsible for dominant, recessive, and X-linked forms of OI have been described.[5] The COL1A2 gene has approximately 600 variants. According to the international database on OI, most of the variants in the *COL1A2* gene are missense, accounting for approximately 74% of the cases.[8]

The only consistent genotype–phenotype correlation is with *COL1A1* variants causing haploinsufficiency of the collagen type 1 α1 chain associated with OI type I.[9] Besides *COL1A1* and *COL1A2*, genetic variants are primarily associated with moderate to severe phenotypes with some exceptions.[10]

To our knowledge, no previous published studies have addressed the clinical features and genetic variants of patients with OI from the United Arab Emirates (UAE). Our study aimed to describe the variant spectrum and genotype–phenotype correlations in patients with OI seen in Tawam Hospital, a tertiary hospital in the UAE.

Methods

This study was approved by the Tawam Medical Human Research Ethics Committee (Ref. No.: AA/AJ/809). It is a descriptive retrospective study of all patients with OI who the clinical geneticists assessed between January 2010 and December 2021 in Tawam Hospital, UAE. The authors retrieved all the data from each patient's electronic medical record, including baseline characteristics, detailed history, three-generation family history, and detailed clinical examination involving hearing test and ophthalmological examination looking at skeletal and extraskeletal manifestations. Radiological investigations, including echocardiogram, skeletal X-ray, and dual X-ray absorptiometry (DXA) scan, and the results of genetic tests were included. The genetic tests were done based on the clinical phenotypes of the patient and family history, including targeted variant testing, next-generation sequencing, and whole-exome sequencing (solo or trio). All identified variants were confirmed by Sanger sequencing. All variants are categorized into five classes (pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign) using the American College of Medical Genetics and Genomics (ACMG) guidelines for classification and by ClinVar, provided family history and clinical information are used to evaluate identified variants for their pathogenicity. Consent for genetic tests was obtained upon evaluations by the clinical geneticists. Data were analyzed and represented using Microsoft Excel 2022.

Results

A total of 40 patients with OI were found and included in this study. Thirty-seven patients had performed genetic tests. The remaining three patients who did not (due to financial/insurance issues) were included in the baseline patient demographics and clinical features but not in molecular analysis.

Patients' Demographics

Our cohort study revealed 40 patients with OI. The youngest patient was diagnosed at birth, while the oldest was at 37 years. Seventeen (42.5%) were males and 23 (57.5%) were females. Consanguinity was documented in nine patients (24.3%). The majority of the studied patients were Emirati (32, 80%). A positive family history of OI was found in 21 patients (52.5%). Positive molecular diagnosis was found in 37 patients (92.5%), and those were of interest to this study.

Molecular Analysis

Thirty-seven (92.5%) patients had positive molecular testing; 28 patients (75.67%) had an autosomal dominant inheritance, and 9 patients (24.3%) had an autosomal recessive inheritance. No patients with X-linked variants were found in this study. A total of four variants reported here were novel (►**Table 1**). The type of variants found in this study included 24 missense, 2 nonsense, 5 frameshift, 3 deletion, and 3 splice site variants (►**Fig. 1**).

►**Table 1** summarizes all variants found in this study. The most commonly identified gene was *COL1A1* (57%), followed by *COL1A2* and *FKBP10* (12.5% each; ►**Fig. 2**). In the *COL1A1* gene, the variant most frequently identified was c.3235G > A (p.Gly1079Ser), followed by c.1249C > G (p.Pro417Ala).

The novel variants found in this study include c.3272delG in the *COL1A1* gene, variant c.972dup (p.G325fs) in *FKBP10* gene, and variant c.2056–1G > A in intron 14 of *LEPRE1* gene. Chromosomal microdeletions encompassing genes causing OI were found in two patients; both patients had a two-copy loss of chromosomal region chr9:108484798–108484918 encompassing exon 4 of the *TMEM38B* gene.

The rest of the variants with minor contributions to OI in the UAE are illustrated in ►**Table 1**.

Clinical Features

The majority (85%) of the studied patients had skeletal phenotypes in the form of fractures, bone deformity, short stature, joint laxity, scoliosis, and low bone density. Patients carrying variants in the *COL1A1* and *COL1A2* genes exhibit a spectrum of age-related manifestations, often correlated with familial predisposition manifested with a family history of the disease. The phenotypic variability encompasses a broad range, from early-onset presentation with recurrent fractures and diminished bone density to delayed onset with osteoporosis.

The extraskeletal phenotypes reported in the studied patients were blue sclera, dentinogenesis imperfecta, hearing loss (22.5%), and dysmorphic features. Only one patient (2.5%) had mitral valve prolapse (►**Table 1**). Patients with variants in the *LEPRE1* gene were found to show early and severe phenotypes marked by clinical signs of OI, such as antenatal fractures, severe scoliosis, bone deformity, and short stature. On the other hand, patients with *TMEM38B* gene variants had variable presentations; one patient presented with antenatal manifestations and dysmorphic features, while another patient had only short stature and blue sclera. The predominant features noted in this study were blue sclera, short stature, scoliosis, and severe low bone density below expected for age in the DXA scan.

Other clinical manifestations of interest that were not reported or documented in the studied patients' charts included basilar invagination, macrocephaly, coxa vara, olecranon apophyseal avulsion, codfish vertebra, and pulmonary complications.

Discussion

To our knowledge, this is the first study to correlate the genotype and phenotype of OI patients from the UAE. This study shows a predominance of pathogenic variants in the *COL1A1* gene (57%), with variant c.3235G > A (p.Gly1079Ser) being the most frequently detected. This could be due to the inclusion of a cluster of familial cases, or this variant could be a founder variant among the UAE population. This is followed by pathogenic variants in *COL1A2* and *FKBP10* genes (12.8% each).

It is worth mentioning here that the variant c.1249C > G (p.Pro417Ala) in the *COL1A1* gene (https://www.ncbi.nlm.nih.gov/clinvar/variation/284534/) and the variant c.2456G > A (p.Arg819His) in the *COL1A2* gene are classified as likely benign and as of uncertain significance in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/variation/360962/). However, given the fact that the studied patients here showed phenotypes that fit with OI, we can consider these variants as possibly or likely causative variants.

It is well known that collagen type I pathogenic variants reflect the dominant variants associated with OI worldwide, with variable percentages that range between 60 and 90% as reported previously.[11] Our finding is almost close to the reported findings from Ukraine (63%),[12] Turkey (62.4%),[13] Taiwan (51%), Korea (52%), and Vietnam (59%).[14–16] A lower proportion of collagen type I pathogenic variants were reported in Russia (41%).[17] On the other hand, reports from Europe showed a higher proportion of those variants, 87% from Sweden and Estonia.[18,19] Asian populations from Japan and China also showed a high proportion of *COL1A1/A2* variants (73.3 and 97.7%, respectively).[20,21]

In Saudi Arabia, 64% of OI-reported cases were secondary to autosomal recessive variants.[22] Similarly, in the Palestinian population, where the consanguinity rate is estimated to be 40%, around 60% of reported cases were due to autosomal recessive forms of OI.[23]

Despite the fact that UAE has a high prevalence of autosomal recessive (AR) disorders due to the high level of consanguinity (54%),[24] our study found that only 24.3% of OI cases are due to AR variants, which is lower than the reported percentages in Saudi Arabia and Palestine.

The phenotype of the identified genetic variants in our patients in this study is consistent with the phenotypic features and presentations reported in previous studies, that is, ranging from mild to severe OI.[25] The most common skeletal manifestations reported here are recurrent fractures, short stature, scoliosis, and low bone density and bone deformity. This is almost similar to what is already known about OI skeletal manifestations. The extraskeletal

Table 1 Summary of variants detected in studied samples

	Demographics				Phenotypical features			Genetic results
Pt	Gender	Ethnicity	Family history	Age at diagnosis	Fracture frequency	Lumbar *Z*-score	Physical features around time of diagnosis	Variant in gene
1	Female	UAE	Yes	26 y	None	−2.8	Lax joints, short stature	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
2	Female	UAE	Yes	3 mo	1 in 3 y	NA	Blue sclera, lax joints, short stature, scoliosis, dentinogenesis imperfecta	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
3	Female	UAE	Yes	2 y	None	−3.3	Blue sclera	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
4	Male	UAE	Yes	12 mo	None		Blue sclera, hearing loss, scoliosis, dentinogenesis imperfecta, lax joints	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
5	Male	UAE	Yes	37 y	NA		Blue sclera	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
6	Male	UAE	Yes	NA	NA	−1.9	Hearing loss	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
7	Female	UAE	Yes	26 y	NA	−2.7	Normal	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
8	Female	UAE	Yes	23 y	NA	−2.3	Blue sclera	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
9	Female	UAE	Yes	16 y	NA	−3.1	Short stature, joint laxity, hearing loss, blue sclera	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
10	Male	Egypt	No	1 mo	4 in 3 mo		Short stature, blue sclera	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
11	Male	UAE	Yes	4 mo	None		Blue sclera, short stature	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*

Table 1 (*Continued*)

	Demographics				Phenotypical features			Genetic results
Pt	Gender	Ethnicity	Family history	Age at diagnosis	Fracture frequency	Lumbar *Z*-score	Physical features around time of diagnosis	Variant in gene
12	Female	UAE	Yes	Birth	NA		Blue sclera, joint laxity, short stature, dentinogenesis imperfecta	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
13	Female	UAE	No	2 y	NA	−1	Hearing loss, short stature	Heterozygous c.3235G > A (p.Gly1079Ser) in *COL1A1*
14	Female	UAE	No	9 mo	3 in 1 y	−7	Hearing loss	Heterozygous c.1249C > G (p.Pro417Ala) in *COL1A1*
15	Male	UAE	No	37 y	3 in 37 y	−2.6	NA	Heterozygous c.1249C > G (p.Pro417Ala) in *COL1A1*
16	Female	UAE	Yes	14 y	NA	−0.5	Normal	Heterozygous c.1249C > G (p.Pro417Ala) in *COL1A1*
17	Male	UAE	Yes	2 mo	None	−0.7	Normal	Heterozygous c.1249C > G (p.Pro417Ala) in *COL1A1*
18	Female	UAE	Yes	3 mo	NA		Normal	Heterozygous c.1249C > G (p.Pro417Ala) in *COL1A1*
19	Male	UAE	No	3 y	7 in 3 y	−3.1	Blue sclera	Heterozygous c.104–2A > G in COL1A1
20	Female	UAE	No	24 y	NA	−3.1	Dysmorphic features, blue sclera, hearing loss, dentinogenesis imperfecta, lax joints	Heterozygous c.3076C > T (p.Arg1026Ter) in *COL1A1*
21	Female	Yemen	Yes	1 mo	3 in 2 y	−3.4	Blue sclera, short stature	Heterozygous c.3076C > T (p.Arg1026Ter) in *COL1A1*
22	Male	Syria	No	4 y	7 in 4 y	−2.1	Blue sclera, hearing loss, lax joints	***Heterozygous c.3272delG in COL1A1***
23	Female	Sudan	No	NA	NA	–-2.1	Short stature	Heterozygous c.4237G > A (p.Asp1413Asn) in *COL1A1*

(*Continued*)

Table 1 (*Continued*)

	Demographics				Phenotypical features			Genetic results
Pt	Gender	Ethnicity	Family history	Age at diagnosis	Fracture frequency	Lumbar *Z*-score	Physical features around time of diagnosis	Variant in gene
24	Male	UAE	No	34 y	None		NA	Heterozygous c.1127G > T (p.Gly376Val) in *COL1A2*
25	Male	UAE	No	8 y	2 in 8 y		Normal	Heterozygous c.1127G > T (p.Gly376Val) in *COL1A2*
26	Male	UAE	No	Birth	Antenatally	−7.1	Blue sclera, hearing loss	Heterozygous c.2456G > A (p.Arg819His) in *COL1A2*
27	Male	UAE	No	3 y	2 in 3 y	−1.8	Normal	Heterozygous c.910G > A (p.Gly304Ser) in *COL1A2*
28	Female	UAE	No	1 mo	5 in 1 mo		Blue sclera, hearing loss, mitral valve prolapse	*Heterozygous c.1505G > A (p.Gly502Asp) in COL1A2*
29	Male	UAE	Yes	2 wk	4 in 5 mo		Dysmorphic features, short stature, scoliosis	Homozygous c.831dup (p.Gly278fs) in *FKBP10*
30	Female	UAE	No	Birth	Antenatally		Blue sclera, short stature	Homozygous c.831dup (p.Gly278fs) in *FKBP10*
31	Female	UAE	No	6 y	None	−6	Short stature, scoliosis	***Homozygous c.972dup (p.G325fs) in FKBP10***
32	Male	UAE	No	16 mo	None		Normal	Homozygous c.1034dup (p.His346fs*27) in *FKBP10*
33	Female	UAE	Yes	2 mo	2 in 2 mo		Blue sclera, short stature	Homozygous c.354del (p.Ile118fs) in *FKBP10*
34	Female	Yemen	Yes	9 y	NA		Short stature, blue sclera	***Two-copy loss on long arm of chr9 encompassing exon 4 of TMEM38B***
35	Female	Yemen	No	Birth	Antenatally		Dysmorphic features, short stature	***Large 2 copy loss on long arm of chr9 encompassing exon 4 of TMEM38B***

Table 1 (*Continued*)

	Demographics				Phenotypical features			Genetic results
Pt	Gender	Ethnicity	Family history	Age at diagnosis	Fracture frequency	Lumbar Z-score	Physical features around time of diagnosis	Variant in gene
36	Female	UAE	Yes	Birth	Antenatally	−8.2	Blue sclera, short stature, bone deformity, scoliosis	*Homozygous c.2056–1G > A in intron 14 of LEPRE1*
37	Female	UAE	Yes	Birth	Antenatally	−4.1	Short stature, scoliosis, bone deformity	*Homozygous c.2056–1G > A in intron 14 of LEPRE1*
38	Female	UAE	Yes	Birth	Antenatally		Short stature	No genetic testing
39	Male	Egypt	No	7 y	3 in 7 y	−4.1	Blue sclera	No genetic testing
40	Male	India	No	8 y	NA	−6.2	Dysmorphic features, short stature	No genetic testing

Abbreviation: NA, not available.
Note: Variants in italics and bold font are the novel variants reported in this study.

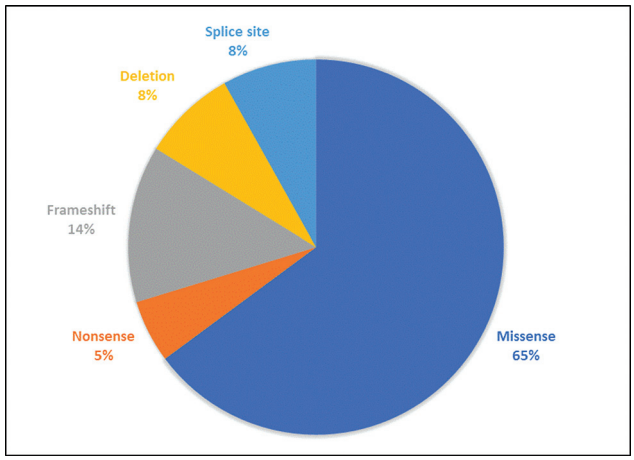

Fig. 1 Variant types found in the studied population in this study.

manifestations of OI were not highly reported in our studied population, that is, 22.5% with hearing loss and 2.5% with mitral valve prolapse, while no pulmonary complications were reported. This is lower compared with the extraskeletal manifestations reported from Saudi patients with OI, where 53% hearing loss, 26% congenital heart malformations, and 70% restrictive lung disease were observed.[26]

Our findings can be explained by the predominance of young patients in our cohort as hearing loss and cardiac and pulmonary complications are known to present more in adulthood. The other possibility is that it is underestimated in our patients due to a lack of adherence to surveillance screening protocols for extraskeletal manifestations.

Our patients showed phenotypes consistent with OI type IV due to variable presentations, mild to moderate in severity (►**Table 1**). None of our patients had lethal phenotypes. The phenotypic severity has been correlated to the affected gene, helical location, resulting residue, and predicted final protein product[21]; however, phenotypic variability is broad, and the full extent of genotype–phenotype correlations remains to be elucidated. Interestingly, variants in the majority of the newly described OI genes are associated with phenotypes

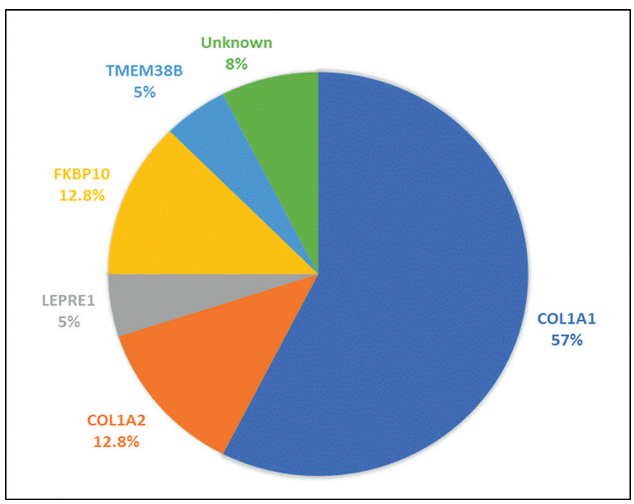

Fig. 2 Frequency of disease-causing variants according to affected genes.

that cannot clinically be distinguished from those described by the traditional classification.[21]

The main limitations of our study include single-center data, which contributed to the small sample size, and it is a retrospective study with the possibility of missing reported clinical features or missed follow-ups. Therefore, further prospective multicenter larger studies are recommended for proper assessment of all skeletal and extraskeletal manifestations as well as longer follow-ups for complication surveillance and management based on different causative variants.

Authors' Contribution

All the authors contributed to the concept and design of the study. A.Q.A.Z. collected data. A.Q.A.Z. and A.A.S. reviewed and analyzed the data, and drafted the manuscript. All the authors contributed to the acquisition of data and revision of the manuscript, and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Ethical Approval

This article does not contain any studies with human participants or animals. This study is approved by the Tawam Human Research Ethics Committee (Ref. No.: AA/AJ/809).

Informed Consent

Written informed consent was obtained during clinical evaluations to proceed with genetic tests.

Conflict of Interest

None declared.

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