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Original Article

# Mutational Analysis of Osteogenesis Imperfecta (OI) in Consanguineous Pakistani Families

**Feroz Khan[1,3], Jalander Shah[2], Bakht Ullah[3], Zunain Khan[3], Sohail Khan[3], Ammara Khan[1], Hajra Afeera Hamid[4], Ihsan Ullah[5], Matiullah[6], Abida Arshad[1*]**

[1]Department of Zoology, Wildlife and Fisheries, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan.

[2] Department of Zoology, University of Lakki Marwat, Khyber Pakhtunkhwa, Pakistan.

[3]Department of Zoology, University of Science and Technology, Bannu, Khyber Pakhtunkhwa, Pakistan.

[4]Department of Medical Lab Technology, University of Science and Technology, Bannu, Khyber Pakhtunkhwa, Pakistan.

[5]Dpartment of Botany, University of Lakki Marwat, Khyber Pakhtunkhwa, Pakistan.

[6]Department of Botany, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan.

**Corresponding author: Abida Arshad**
**Email:** abida.arshad@uaar.edu.pk

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## Abstract

Brittle bone disease, or Osteogenesis Imperfecta (OI), is a heritable genetic disorder marked by severe bone fragility, osteoporosis, and low bone mineral density. This study investigated consanguineous Pakistani families showing autosomal recessive inheritance of OI. Blood samples (5–10 ml) were collected from both normal and affected individuals, including three normal and one affected member from Family A, and three normal and three affected members from Family B. Genomic DNA was extracted using the conventional phenol–chloroform method. Whole exome sequencing was performed for one affected individual (IV-5) and two obligate carriers (III-1 and III-2) from Family A to identify causative genes. Sanger sequencing was used to validate gene variants consistent with the patients' clinical phenotypes and to determine segregation within the families. The analysis identified pathogenic variants in CREB3L1 (c.528C>T; p. Leu346Asp) and COL1A1 (c.540G>A; p. Leu133*) using specifically designed primers. Exome data were further filtered for homozygous variations using moon analysis, based on the autosomal recessive pattern of the disorder. Several genes with clinical features corresponding to the study subjects were reported. Overall, these findings are valuable for carrier detection and genetic counseling to help prevent transmission of the disease to future generations.

**Keywords:** Sanger Sequencing, Segregation, Abnormality, Autosomal Recessive, Disorder.

## Introduction

Skeletal dysplasia and bone fragility are hallmarks of osteogenesis imperfecta (OI), are genetic disorders of connective tissues that is often referred to as brittle bone disease.

Lobstein disease or Vrolik syndrome has a reported incidence of 1 in 15,000 to 20,000 births, respectively, and is ca used by an anomaly in the metabolism of type I collagen (Deguchi *et al*., 2021). There is considerable variation in the severity of OI and its associated symptoms, making it a clinically and genetically diverse disorder with a broad range of inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked modes of transmission (Zhytnik *et al*., 2020). Eighty-five to ninety percent of OI cases are produced by physical pathogenic polymorphisms in the gene programming collagen *COL1A1* and *COL1A2*.

A variety of skeletal and extra-skeletal manifestations can result from changes in the arrangement of the collagen type 1 molecule, which has significant effects on a wide range of tissues, including the dermis, cartilage, dentine, cornea, ligaments, tendons, and bone (Sałacińska *et al*., 2021). A triple helix arrangement with spherical amino and carboxy terminal properties makes up procollagen type I, the precursor of type I collagen. The carboxy-terminal property is crucial for the common identification and is required of collagen chains (Claeys *et al*., 2021). Studies on mice with OI show encouraging results, including a substantial increase in bone mineralization and collagen, which improves bone structure and lowers the risk of fractures (Lang & Semon, 2023).

## Review of Literature

The identification of the genes and molecular pathways behind OI has advanced significantly in recent decades. The traditional clinical classification of silence is now somewhat obsolete, and genetic counseling is made more difficult by the presence of distinct inheritance patterns and the involvement of various causal genes. However, genetic classification offers the possible expansion of genotype-based medicinal techniques and enables a precise documentation of inheritance for family development (Panzaru, Florea, Caba, & Gorduza, 2023).

OI current treatments are insufficiently effective, and numerous studies have concentrated on creating highly targeted treatments to enhance poor bone mineral density and the underlying bone fragility in those who are afflicted, which may have an impact on the results. Although they require more research, other novel potential treatments for OI, including mesenchymal stem cells, sclerostin inhibitory antibodies, recombinant human parathormone, and gene treatment, demonstrated encouraging outcomes both in vivo and vitro in animal simulations or human preparation (Dinulescu *et al.*, 2024). In the present research, we have examined two Pakistani cousin marriage families of OI in an autosomal recessive arrangement of inheritance.

## Materials and Methods

### *Ethical Approval and Family Recruitment*

The Institutional Review Board (IRB) of Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan, granted approval for the current study (PMAS-AAUR/D. FoS/269). All participants signed a written informed consent form that was approved by the IRB. Radiographs and pictures of the afflicted people were gathered in the local governmental hospital. A total of two families were studied, among these one family (A) was collected from the district Karak and the other family (B) from Tehsil Domel district Bannu, Khyber Pakhtunkhwa province of Pakistan.

### *Blood Sampling and Genomic DNA Extraction*

5 to 10 ml of peripheral blood was taken from normal and abnormal members of the family. Blood samples of family A were obtained from three normal individuals (III-1, III-2, and IV-1) and one affected member (IV-2), respectively. Similarly, family B contains three normal (III-1, IV-2, and IV-10) and three abnormal members (IV-4, IV-5, and IV-

7). The Gene Elute Blood Genomic kit (Sigma-Aldrich, Cat 2010-1, St. Louis, USA) and the conventional phenol chloroform procedure were used to extract genomic DNA from the drawn blood.

### *Whole Exome and Sanger Sequencing*

To detect the mutated genes in these families, whole exome sequencing of an abnormal individual (IV-5) and two obligate carriers of family A (III-1 and III-2) respectively. The Twist Human Core Exome kit (Twist Bioscience, South San Francisco, CA, USA) was used to prepare the sample. The Novaseq 6000 sequencing platform (Illumina, San Diego, CA, USA) was used for the sequencing. An automated Galaxy-based pipeline that was developed internally was used to analyze the data. The Genome Analysis Toolkit Unified Genotyper was used to call variants. Variant DB and ANNOVAR were used to annotate the variants. The reference build was GRCh37. Diploid used the Moon software program, which is available online, to analyze the so-called variations. The program generates a shortlist of variants that could be the cause of the disease using the VCF file and the patient's gender, age of onset, and entered HPO terms. Sanger sequencing was used to confirm gene variants that matched the patient's phenotype and to determine whether any family members had the condition.

## Results and Findings

### *Clinical Analysis*

According to the pedigree's design, the affected members' parents were normal, but their siblings had OI condition and showed a consanguineous, autosomal recessive inheritance pattern. Table 1 displayed the clinical characteristics of the impacted family members. As seen in figures 1& 2, most afflicted members have many fractures, upper and lower extremity bending, blue sclera, and weak bones.

**Table 1**

*Clinical features of affected individuals of families*

| | Affected individuals | | | | | |
|---|---|---|---|---|---|---|
| | Family A | | Family B | | | |
| **Clinical features** | **IV-2** | **IV-5** | **IV-4** | **IV-5** | **IV-6** | **IV-7** |
| Gender | Female | Male | Male | Male | Male | Male |
| Age (Years) | 20 | 28 | 13 | 26 | 28 | 22 |
| Multiple fractures | + | - | + | + | + | + |
| Vertebral fractures | - | + | - | - | - | - |
| Bowing of upper extremities | + | + | + | + | - | - |
| Bowing of lower extremities | + | + | - | + | - | - |
| Shortening of lower extremities | + | - | - | - | - | - |
| Shorting of upper extremities | + | - | - | + | + | - |
| Color of sclera | + | - | + | + | - | + |
| Dentinogenesis imperfecta (DI) | + | - | - | - | + | + |
| Hypermobility of joints | - | + | - | + | - | + |
| Cardiac impairment | - | - | - | + | - | - |
| Hear impairment | + | + | - | - | - | - |
| Intellectual disability | + | - | - | - | - | - |

+=Present, -=Absent.

**Figure 1**

*(S): A four-generation pedigree constructed consanguineous autosomal recessive of OI. Males are denoted by a square and females are denoted by a circle. Abnormal individuals are denoted by black filled symbol, while normal individuals are denoted by*

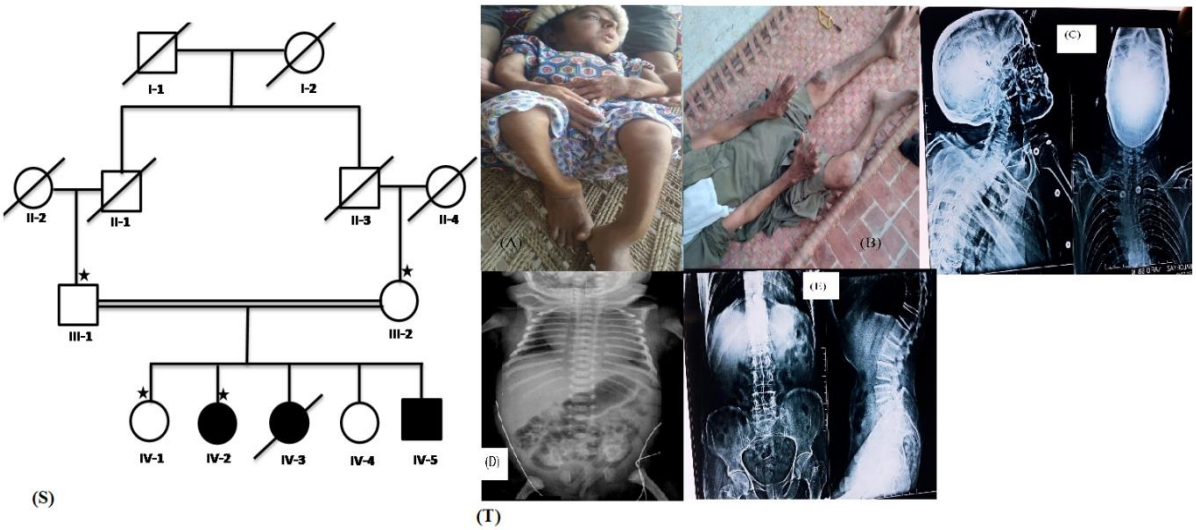
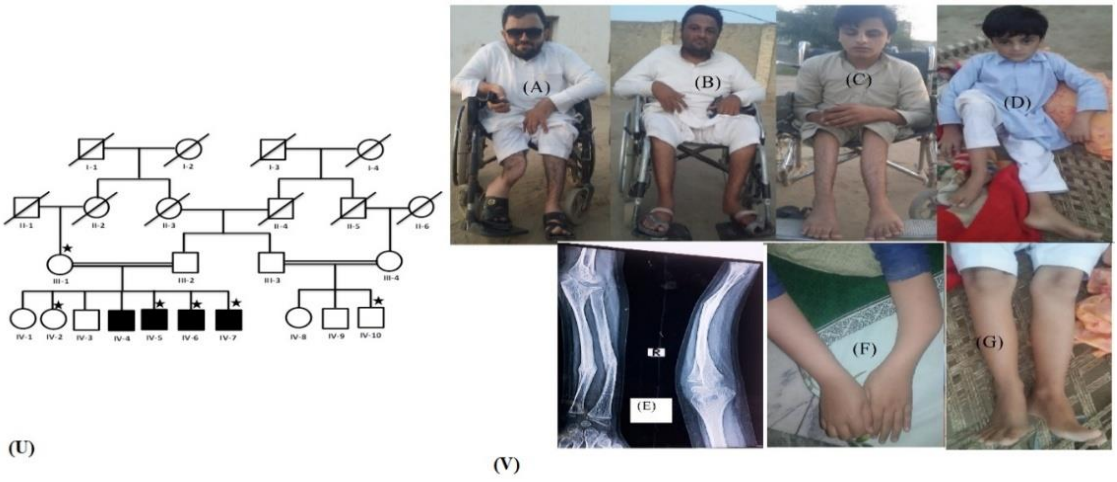



**Figure 2**

*(U): Four-generation pedigree, constructed, autosomal recessive of OI. Males are denoted by a square, and females are denoted by a circle. Abnormal participants are denoted by a black sign, while healthy participants are denoted by a clear one. Intersect*




**Genetic Analysis**

The WES of the (IV-5, III-1, and III-2) affected members have done and lastly reported different variants in their DNA. Configuration was done with BWA15, and the causative variants were called with genomic assessment. Illumina Variant Studio v2.2 was used to annotate each of the variations. Using links from http://www.diploid.com/moon for moon analysis, exome data were filtered for homozygous variations based on the computation of the autosomal recessive type of the disease. analysis based on the OI-related gene's expression and

function. After analysis, different genes are reported, and clinical phenotypes of the analyzed genes were like the present study and designed primers (5'GGGATTACAGTTGGAACGTCA3', 5'CTGGTCTAGCTGACTGACTG3') for family A, while (5' CGCTGGACCCTATCTTGG3', 5'TCCTCCGGGCTTAAGACC3') for family B. The reported genes *CREB3L1* (c.528C>T; p. Leu346Asp) and *COLIA1* (c.540 G>A, p. (Leu133*) by spending precise segregated in both healthy and abnormal participants of the family were shown in Figures 3&4.

**Figure 3**

*The Sanger sequencing of the COLIA1 indicated the carrier was normal and affected members of the family A, but was not co-segregated. A homozygous mutation (c.540 G>A, p. (Leu133*) reported in patient or (G/A).*

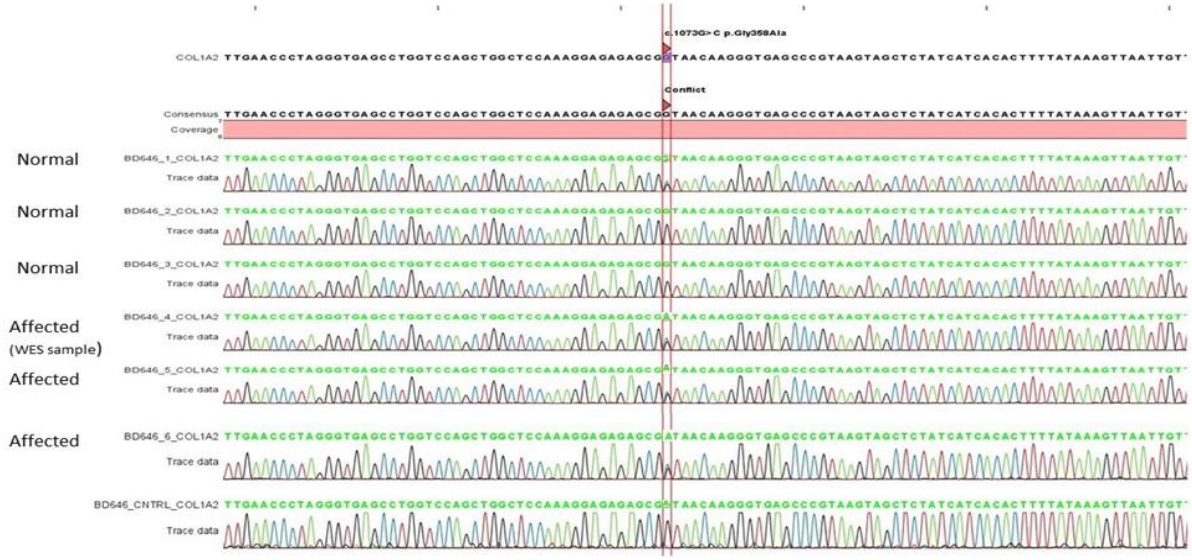



**Figure 4**

*Sanger sequencing of the CREB3L1 gene indicated the carrier was normal and affected members of the family B, but was not co-segregated. A homozygous mutation (c.528C>T; p. (Leu346Asp) reported in a patient or (C/T).*

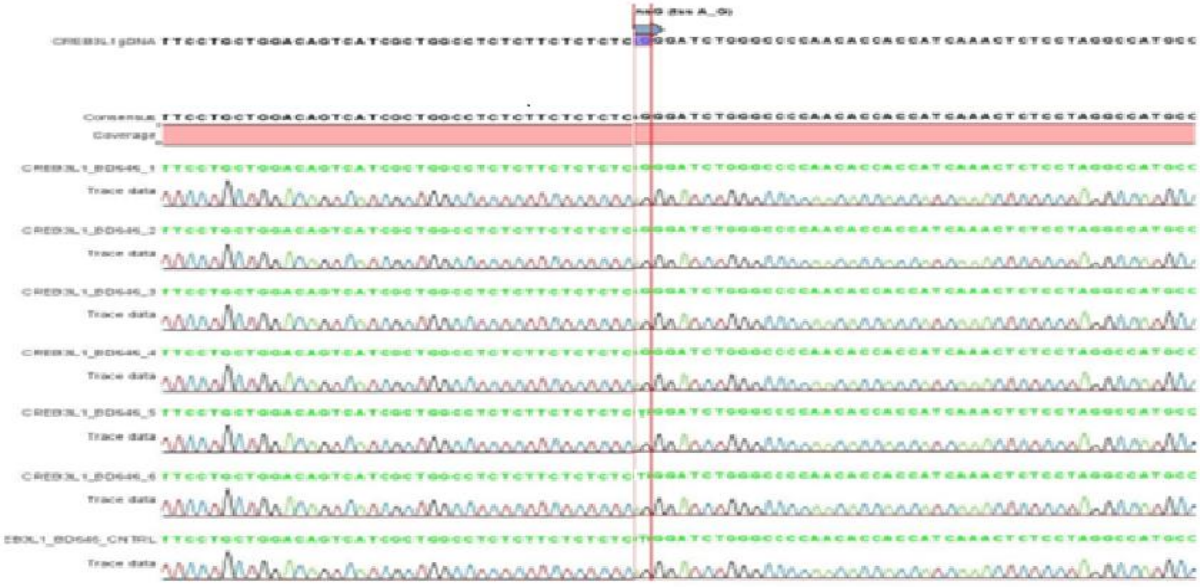


**Table 2**

*To Date List of Previous Mutations Reported in COLIA1 Gene.*

| S. No | Mutations | Mutation type | Ethnic origins | References |
|---|---|---|---|---|
| 1. | c.2461G > A p.(Gly821Ser<br>c.1299 + 1G > A<br>c.3118G > A p.(Gly1040Ser)<br>c.2075G > C p.(Gly692Ala)<br>c.2075G > C p.(Gly692Ala)<br>c.4292C > T p.(Thr1431Ile) | Splice site/<br>Nonsense | Sweden | [8] |
| 2. | c.3531+1G>T, c.3226G>A p.(Gly1076Ser), c.3567del p.(Gly1190Valfs*49), c.2426dup1 p.(Ala811Cysfs*10) c.4237G>A p.(Asp1413Asn), c.3118G>A p.(Gly1040Ser)<br>c.1200+1G>A,c.3749del p.(Gly1250Alafs*81),c.3567del p.(Gly1190Valfs*49),c.189C>Ap.(Cys63*),c.1299+1G>A<br>Splice site/ Frame shift, Palestine | | | [9] |
| 3. | c.144delTp.His48GlnfsX26, c.157-158delTG p. Trp53GlufsX19<br>c.268G>Tp.Glu90X, c.433_434insC p. Gly145AlafsX24<br>c.441dupCp.Gly148ArgfsX21, c.484C>Tp.Gln162X<br>c.569delCp.Pro190LeufsX75,c.573_574delCCinsG<br>p.Pro193LeufsX72,c.579delTp.Gly194ValfsX71,c.643-2A>G<br>c.757C>Tp.Arg253X, c.769G>Ap.Gly257Arg, c.769G>A<br>p.Gly257Arg,c.898C>Tp.Gln300X,c.903+1G>A,c.1121G>C<br>p.Gly374Ala,c.1128delTp.Gly377AlafsX164,c.1155+1G>A<br>c.1200+1G>A,c.1243C>Tp.Arg415X,c.1299+1G>A,c.1299+1G>A,c.1522G>Ap.Ala508Thr,c.1588G>Ap.Gly530Ser<br>c.1678G>T p.Gly560Cys,c.1787G>Cp.Gly596Ala<br>c.1866delTp.Gly623AlafsX143,c.1930-2A>C,c.2183G>A<br>p.Gly728Glu,c.2297C>Gp.Thr766Ser,c.2299G>A<br>p.Gly767Ser,c.2410G>Tp.Glu804X,c.2450delC<br>p.Pro817LeufsX291,c.2461G>Ap.Gly821Ser,c.2560G>Ap.Gly854Ser,c.2775delT<br>p.Gly926ValfsX182,c.2867G>C<br>p.Gly956Ala,c.3076C>Tp.Arg1026X,c.3328delC<br>p.His1110ThrfsX129,c.3559G>Tp.Gly1187Cys<br>c.3638delGp.Gly1213Alafsx26,c.3655G>Ap.Asp1219Asn<br>c.3893C>Tp.Thr1298Ile,c.4363G>Ap.Gly1455Ser<br>Missense/Nonsense/Splice site/Frame shift, China | | | [10] |

**Table 3**

*To Date List of Previous Mutations Reported in CREB3L1 Gene*

| S. No | Mutations | Mutation type | Ethnic origins | References |
|---|---|---|---|---|
| 1. | c.911C>T<br>p.Ala304Val | Missense | Turkey | [11] |
| 2. | c.1365del<br>p.Pro458Argfs*25 | Frame shift | Indonesia | [12] |
| 3. | c.1284C > A<br>p.Tyr428*, | Nonsense | Sweden | [8] |
| 4. | c.934_936delAAG<br>p.Lys312del | Frame shift | USA | [13] |

## Discussion

OI is an inherited genetic abnormality considered by reduced bone mineral density. There are various types of OI with various symptoms that range from mild to severe. Everyone with this condition may have a variety of symptoms. In the present research, we have examined the two cousin marriages in Pakistani families of OI containing bone fragileness, bending of legs and hands, and bones with recessive design of inheritance. Whole exome sequencing (WES) monitored by Sanger sequencing recognized homozygous variants in two genes like *COLIA1* and *CREB3L1,* respectively.

The *COL1A2* translates the α2-chain of type 1 collagen, including different trimeric proteins containing two α1-chains (translated by *COL1A1*) and one α2-chain. Type 1 collagen is the most plentiful form of collagen in humans and behaves as the main important protein of different organs like skin, bones, cartilage, and the cornea of the eyes. Five pathogenic variants were found in the *COL1A1* gene and two in the *COL1A2* gene, conferring to the genetic analysis. Crucially, none of these pathogenic variants has ever been documented in the literature before. Among these are one new heterozygous missense pathogenic variant in *COL1A2* (c.596G>T) and two new heterozygous frameshift pathogenic variants in *COL1A1* (c.2890_2893del and c.3887del) (Paduano, Fischetto, Moretti, De Vito, & Tatullo, 2023). A homozygous nonsense pathogenic mutation in *CREB3L1*, p.Tyr428*, c.1284C>A in one boy, earlier recognized with OI type III. *COL1A1* and *COL1A2* were two genes among persons that supported a disease-causing variant. We establish uncommon variations with unidentified impact in numerous other genes associated with tooth growth (Andersson et al., 2020). Knockout of *CREB3L2* in mice caused serious chondrodysplasia due to the collapse to produce type II procollagen, with the resulting of interruption of hypertrophic region construction in cartilage soft tissue. Type II collagen and other cartilage pattern proteins are stored in the ER membrane of *CREB3L2* chondrocytes. The protein creation of *CREB3L2* improves transcription of *SEC23A,* which translates a module of the COPII complex. In human being dermal fibroblast cells, *CREB3L2* knockdown inhibited *SEC23A* expression and triggered the irregular cisternae shape of the Golgi apparatus (irregularly curved cisternae and aggregation), symptomatic difficulties with subcellular operating (Saito *et al*., 2009). Genetic and cellular evaluation of *CREB3L1* knockout mice showed analogous cellular and soft tissue features in bone, as compared to cartilage. *CREB3L1* primary osteoblast cells had enlarged the ERs filled with bone matrix proteins, and there was a considerable decrease in collagen substance in the bone pattern, resulting to serious osteopenia and fractures (Keller *et al*., 2018).

## Conclusion

The consanguineous OI families in Pakistan with an autosomal recessive inheritance pattern must be examined in the current investigation. Following WES and Sanger sequencing, two genes were found to have mutations, such as *CREB3L1* (c.528C>T; p.Leu346Asp) and *COLIA1* (c.540 G>A, p. (Leu133*). These were reported using particular primers, which showed that the affected and control members of the family were segregated. To prevent the disease from being passed down to the following generations in this family, the study will be useful for carrier testing and genetic counseling.

## Limitations

1. **Small Sample Size:** The study includes a limited number of families, which may not fully represent the genetic diversity of OI in the broader Pakistani population.
2. **Focused on Two Families Only:** Findings are based on specific consanguineous families; results may not be generalizable to non-consanguineous or ethnically diverse groups.
3. **Limited Functional Validation:** The detected variants were confirmed through sequencing, but detailed functional studies (e.g., protein assays, in vivo models) were not performed to confirm pathogenic mechanisms.
4. **Restricted to Exonic Regions:** Whole exome sequencing does not capture intronic, regulatory, or structural variants that may also contribute to OI.

5. **Resource and Data Constraints:** The study relies on available bioinformatics tools and databases, which may not fully capture novel or population-specific mutations.

## Contributions

1. **Identification of Novel/Relevant Mutations:** The study identifies pathogenic variants in CREB3L1 and COL1A1, enriching the mutation spectrum of OI in the Pakistani population.
2. **Insight into Autosomal Recessive OI:** Provides valuable data on recessive inheritance patterns in highly consanguineous families.
3. **Establishment of Genetic Workflow:** Demonstrates an effective combination of whole exome sequencing and Sanger validation for detecting OI-related mutations.
4. **Foundation for Genetic Counseling:** Offers critical information that can guide families regarding disease transmission and carrier status.
5. **Contribution to Population Genetics:** Adds valuable genetic data that may support future regional or national genetic databases.

## Recommendations

1. **Expand Sample Size:** Future research should include more families from different regions of Pakistan to capture wider genetic variability.
2. **Functional Studies:** Conduct in vitro and in vivo experiments to better understand the biological impact of the identified mutations.
3. **Include Whole Genome Sequencing (WGS):** To detect non-exonic, structural, and regulatory mutations that WES may miss.
4. **Develop Screening Programs:** Implement low-cost carrier screening for high-risk consanguineous populations.
5. **Strengthen Genetic Counseling Services:** Create accessible counseling units in hospitals to educate families on inheritance risks.
6. **Collaborative Research:** Encourage partnerships with international genetics laboratories to enhance diagnostic precision.
7. **Longitudinal Clinical Follow-Up:** Track affected individuals to understand phenotype–genotype correlation more effectively.

## Implications

1. **Public Health Impact:** The findings support early diagnosis and targeted prevention strategies for OI in communities with high consanguinity.
2. **Improved Clinical Management:** Knowing the exact mutations helps clinicians make better treatment and management plans.
3. **Genetic Awareness:** Raises awareness about the role of genetic testing in detecting hereditary disorders in Pakistan.
4. **Guidance for Policymakers:** May inform national policies on premarital screening, genetic counseling, and rare disease management.
5. **Future Research Pathways:** Sets a foundation for future molecular studies on collagen-related disorders and skeletal dysplasia.

## Declarations

*Ethical Approval and Consent to Participate:* This study strictly adhered to the Declaration of Helsinki and relevant national and institutional ethical guidelines. Informed consent was obtained. All procedures performed in this study were consistent to the ethical standards of the Helsinki Declaration. The current study was performed after obtaining

approval from the Institutional Review Board (IRB) of Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan (PMAS-AAUR/D.FoS/269). The IRB-approved written informed consent form was signed by all participating individuals.

*Consent for Publication:* The authors give their consent for publication.

*Availability of Data and Materials:* Upon request, the corresponding author will make the datasets used and/or analyzed during the current investigation available.

*Competing Interest:* The authors have no conflicts of interest to declare

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*Authors' Contribution:* Collecting data, writing the original manuscript: FK; Arranged the data: JS; Described the sequencing analysis: BU; Arranged the Sanger sequencing: ZK; Arranged the sequencing manner of manuscript: SK; Checked the manuscript: AK; Described the clinical analysis: HAH; Pedigree designing: IU; Photograph designing: M; Supervision, review and editing: AA. All authors have reviewed and approved the final version of the paper.

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