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# Molecular genetics analysis of osteogenesis imperfecta in clinical practice

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*Osteogenesis imperfecta (OI) is characterized by fractures with minimal or absent trauma, representing a continuum ranging from perinatal lethality through individuals with severe skeletal deformities to nearly asymptomatic individuals with mild predisposition to fractures. Diagnosis of OI is an interdisciplinary task based on family and/or patient history of fractures combined with characteristic physical findings. Radiographic examination reveals fractures of varying ages and stages of healing, wormian bones, and osteopenia. As there is no definitive test for OI, molecular genetic testing by next generation sequencing (NGS) of COL1A1 and COL1A2 and up to 12 other genes is essential to confirm the genetic background. Therefore, we designed a NGS gene panel comprising 12 genes involved in OI or severe osteoporosis. Here we report results in a cohort of 11 apparently sporadic young patients with OI, all offspring of unaffected parents, who were referred to orthopaedic surgery at Sv. Katarina Special Hospital (Zabok/Zagreb, Croatia). Ten of these 11 patients could be classified genetically. Overall, three genes with different percent relating to the whole cohort were involved: COL1A1 (63.6%), COL1A2 (18.18%) and WNT1 (9.09%).*

**Key words:** osteogenesis imperfecta; molecular genetics - analysis

## INTRODUCTION

Bone fragility with fractures in infancy or childhood has been reported in over 100 genetic disorders from skeletal dysplasia and inborn errors of metabolism to congenital insensitiveness of pain (1). The most common genetic form of bone fragility is osteogenesis imperfecta (OI). The disease is phenotypically and genetically heterogeneous and can manifest in various phenotypes including perinatal lethality, severe and multiple skeletal deformities, severe juvenile osteoporosis, as well as mildly affected individuals (2-4). Despite the direct influence on bone structure, it can be accompanied by numerous symptoms such as blue sclera, deafness, abnormal tooth development, joint hypermobility, increased risk of hernias, capillary fragility, aneurysms, etc. The diagnosis of OI based solely on clinical evaluation may be missed (2). Molecular genetics diagnosis is therefore instrumental for accurate clinical diagnosis.

Treatment for OI is directed at managing the symptoms. A multidisciplinary approach to treatment is essential for children and adults. The goal of all treatments for OI is to minimize fractures, enhance independent function, reduce pain, support mobility, and promote general health. Medication with bisphosphonates, vitamin D and calcium aims at preserving bone mass and strength (3, 4). Physical therapy, fracture care, and orthopedic surgery are approaches for the musculoskeletal aspects of OI. In particular, orthopedic surgery including osteotomy, intramedullary rodding is performed to correct bowing of long bones, support stability, correct the mechanical axis, and stabilize the spine (5).

Osteogenesis imperfecta has been classified into autosomal dominant and recessive forms. More than 90% of OI cases are caused by heterozygous mutations in *COL1A1*

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TABLE 1. Genes and phenotypes involved in osteogenesis imperfecta (OI) and severe osteoporosis

| Phenotype | Mode of inheritance | Gene name, symbol and MIM-number |
|---|---|---|
| Osteogenesis imperfecta (OI) and/or severe osteoporosis | | |
| **OI Type I, IIa, III, IV** | **AD** | **Type 1 collagen α-chain, *COL1A1* gene, MIM*120150,** |
| **OI Type I, IIa, III, IV** | **AD** | **Type 2 collagen α-chain, *COL1A2* gene, MIM*120160** |
| **OI Type IIb and Type VII** | **AD, AR** | **Cartilage associated protein, *CRTAP* gene, MIM*605497** |
| **OI Type V** | **AD** | **Interferon-induced transmembrane protein 5, *IFITM5*, MIM*614757** |
| OI Type VI | AR | Serpin peptidase inhibitor, clade F, member 1, *SERPINF1* gene, MIM*172860 |
| **OI Type VIII** | **AR** | **Prolyl 3 hydroxylase 1, *P3H1*, MIM*610342** |
| OI Type IX | AR | Peptidyl isomerase B (cyclophin B), *PPIB*, MIM*123841 |
| OI Type X | AR | Serpin peptidase inhibitor, clade H, member 1, *SERPINH1*, MIM*600943 |
| OI Type XI, including Bruck syndrome 1 | AR | FK506-binding-protein 10, *FKBP10* gene, MIM*607063 Procollagen-lysine, 2-oxoglutarate 5-diopxygenase 2; *PLOD2* gene, MIM* 601865 |
| OI Type XII | AR | Transcription factor SP7, *SP7* gene, MIM*606633 |
| OI Type XIII | AR | Bone morphogenic protein 1, *BMP1*, MIM*112264 |
| OI Type XIV | AR | Transmembrane protein 38B, *TMEMB38*, MIM*611236 |
| **OI Type XV** | **AR** | **Wingless-Type MMTV integration site family, Member 1, *WNT1*, MIM*164820** |
| OI Type XVI | AR | Chromome 11p11.2 Deletion syndrome, *CREB3L1*, MIM#616229 |
| OI Type XVII | AR | Secreted protein, acidic, cysteine-rich, *SPARC* gene, MIM182120 |
| X-linked form OI | XLD | Membrane bound transcription factor protease S, site 2, *MBTPS2* gene MIM *300294 |
| Severe osteoporosis with bone deformities and fractures in childhood | | |
| **Osteoporosis (-pseudoglioma) syndrome** | **AD** | **Low density lipoprotein receptor-related Protein 5, *LRP5* gene, MIM *603506** |
| **Vitamin D-resistant rickets type IIA** | **AR** | **Vitamin D receptor, *VDR* gene, MIM *601769** |
| **Vitamin D-resistant rickets type I** | **AR** | **25-Hydroxyvitamin D3-1-alpha-hydroxylase, *CYP27B1* gene, MIM *609506** |
| **Hypophosphatasia, infantile, childhood** | **AR** | **Alkaline phosphatase, liver/bone/kidney type, *ALPL* gene, MIM *171760** |
| **Neonatal severe hyperparathyroidism** | **AR, AD** | **Calcium-sensing receptor, *CASR* gene, MIM *601199** |
| **X-linked hypophosphatemic rickets** | **XLD** | **Phosphate-regulating endopeptidase homolog X-linked, *PHEX* gene, MIM *300550** |

Genes in bold are included in the osteogenesis/severe osteoporosis NGS gene panel for the first round of sequence analysis. All the other genes are included in a NGS gene panel for a second screening round.

(type 1 collagen α-chain) or *COL1A2* (type 2 collagen α-chain) and show autosomal dominant inheritance. However, in the last years, a number of genes responsible for both recessive and dominant forms of this condition have been described. Currently, 17 distinct types of OI characterized on the basis of genotypic features are listed in scientific databases (Table 1) (6). For complete molecular genetics analyses of the *COL1A1* and *COL1A2* genes, more than 100 exons have to be analyzed. This is an expensive and time consuming task with conventional Sanger sequencing (7, 8). To be able to cover the complete coding region of the *COL1A1* and *COL1A2* genes, as well as most important other OI and severe osteoporosis causing genes in one analytical run, we decided to employ next generation sequencing (NGS). This new technique combines high performance with significantly lower operation cost and processing time. Massive parallel sequencing with NGS enables analyzing many genes at the same time. Therefore, we designed a NGS gene panel comprising 12 genes involved in OI or severe osteoporosis.

Here we report the results in a cohort of 11 apparently sporadic young patients with OI, all offspring of unaffected, non-related parents, who were referred to orthopedic surgery at Sv. Katarina Special Hospital (Zabok/Zagreb, Croatia).

## PATIENTS AND METHODS

The molecular genetics analysis preceded orthopedic surgery and established the diagnosis of OI. We utilized the IonTorrent PGM next generation platform (Thermo Fisher Scientific, Walham, MA, USA) in our setting for molecular diagnosis of OI. The gene panel was designed with the online tool AmpliSeq Designer from Thermo Fisher Scientific. Technical characteristics of the gene panel are shown in Table 2. DNA preparation from EDTA-blood was performed with Qiagen blood kit (Qiagen, Hilden, Germany) and amplified by multiplex polymerase chain reaction. More than 12 patients can be sequenced together in one analytical run either for the same gene panel or for different gene panels. Figure 1 shows an example of loading map of a chip (316v2)

TABLE 2. Technical characteristics of the next generation sequencing (NGS) panel for osteogenesis imperfecta/severe osteoporosis

| Technical Panel Data | Values |
|---|---|
| Number of genes | 12 |
| Panel size | 66.32 kb |
| Primer Pools | 2 |
| Total number of exons | 213 |
| Total number of amplicons | 351 |
| Amplicon lengths | approximately 200–250 bp |
| Covering | 97.94% |

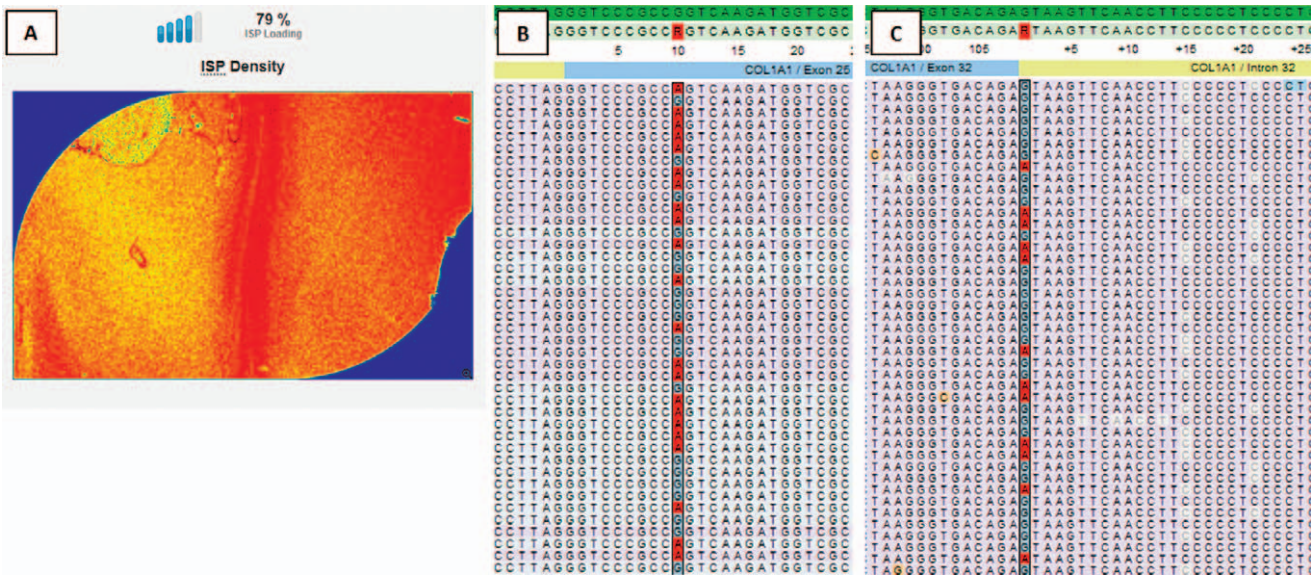


FIGURE 1. A = loading map of a 316v2 chip of the Ion PGM: red indicates the Ion Spheres with bound DNA fragments. Sequence information from the individual patients can be distinguished by an individual 'bar code' sequence ligated to the PCR products. B, C = two examples of variants detected with the software module SeqNext: B = c.1678G>A (p.Gly560Ser) (glycine to serine mutation, patient K.A.) and C = c.2235+1G>A (splice site mutation, patient E.L.).

TABLE 3. Patient clinical phenotype, osteogenesis imperfecta (OI) causing mutations and predicted phenotype based on genotype (het: heterozygous, hom: homozygous)

| Gene | Exon /intron | Variant | Patient ID | | | | | | | | | | | Predicted phenotype | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | E.L. | Y.V. | M.M. | E.S. | L.R. | S.Y. | K.A. | A.D. | N.L. | K.K. | M.V. | | |
| *COL1A1* | Intron 1 | c.104-441G>T | het | - | - | het | het | hom | - | het | - | - | - | Reduced BMD | 21 |
| | Exon 25 | c.1678G>A (p.Gly560Ser) | - | - | - | - | - | - | het | - | - | - | - | OI type I/IV | 13, 15 |
| | Intron 32 | c.2235+1G>A | het | - | - | - | - | - | - | - | - | - | - | OI type III | 13 |
| | Exon 33 | c.2299G>A (p.Gly767Ser) | - | - | - | - | het | - | - | - | - | - | - | OI type III | 16 |
| | Exon 43 | c.3118G>A (p.Gly1040Ser) | - | - | - | het | - | - | - | - | het | - | - | OI type III/ IV | 12, 13, 14 |
| | Exon 44 | c.3226G>A (p.Gly1076Ser) | - | het | - | - | - | - | - | - | - | - | - | OI type III/ IV | 13, 17 |
| | Exon 49 | c.3835A>T (p.Asn1279Tyr) | - | - | - | - | - | - | - | - | - | - | het | OI type III | 18 |
| *COL1A2* | Exon 19 | c.982G>A (p.Gly328Ser) | - | - | het | - | - | - | - | - | - | - | - | OI type III | 19 |
| | Exon 40 | c.2458G>A (p.Gly820Ser) | - | - | - | - | - | - | - | het | - | - | - | OI type III | 20 |
| *WNT1* | Exon 2 | c.212T>C (p.Leu71Pro) | - | - | - | - | - | het | - | - | - | - | - | OI type XV | - |
| | Exon 3 | c.528C>G (p.Phe176Leu) | - | - | - | - | - | het | - | - | - | - | - | OI type XV | - |

used in this study. It serves as a process control and demonstrates the even distribution of the ion spheres loaded with amplified DNA.

For our first round mutation screening panel we included 12 genes known to cause severe destruction of bone architecture in newborn, children and young adults. This panel includes three genes causing autosomal dominant inheritance OI (*COL1A1*, *COL1A2* and *IFITM5*), three genes causing common recessive forms of OI (*CRTAP*, *LEPRE1* and *WNT1*) and six genes causing severe osteoporosis including the juvenile form (*PHEX*, *VDR*, *CYP27B1*, *LRP5*, *ALPL* and *CASR*) (Table 3). Bioinformatic analysis was carried out with the software module SeqNext (SeqPilot™, JSI, Ettenheim, Baden-Württemberg, Germany). All NGS results had a very good quality. Sequences of insufficient quality were repeated with Sanger sequencing.

## RESULTS

### *Mutations in the COL1A1 gene, autosomal dominant inheritance of OI*

Pathogenic mutations were detected in 10 of 11 patients. Seven patients were heterozygous for a pathogenic mutation in the *COL1A1* gene (Table 3). In five of these cases (K.A.,

L.R., E.S., N.L., Y.V.), a glycine residue was mutated to serine in the triple helical region. This essential 3-dimensional structure depends on multiple triplets with the sequence Gly-X-Y where X often is hydroxylated lysine and Y hydroxylated proline (9). Mutations of glycine are the most common pathogenic cause of OI. Two unrelated patients of this group carried the same heterozygous mutation (E.S. and N.L.), which was published before by several authors (10-12). The remaining three glycine to serine mutations in the triple helical region found in our patients (K.A., L.R, Y.V.) were also published before (11-13). All the glycine to serine mutations we found to be related to OI type III, which matched with the clinical diagnosis of our expert team.

One patient (E.L.) displayed a heterozygous splice site mutation in position +1 of intron 32 of the *COL1A1* gene, which leads to a severely compromised protein. Also, this mutation was decribed before with the OI type III (13). For another patient (M.V.), we found a *COL1A1* missense mutation in the N-terminal part of the pro alpha chain region close to a calcium binding site located within in the integrin-C-propeptide interaction region. A mutation at the same codon, but with another amino acid exchange has been reported before with a phenotype of OI type III (12).

### *Mutations in the COL1A2 gene, autosomal dominant inheritance of OI*

For two patients (M.M., A.D.), the NGS analysis revealed heterozygous mutations in the *COL1A2* gene. Like in the *COL1A1* gene, glycine residues located in the triple helical region were mutated to serine. Clinically, we classified both patients as OI type III, which matches with the corresponding phenotype in the scientific literature (13, 14).

### *Mutations in the WNT1 gene, autosomal recessive form of OI*

For one of our 11 patients (S.Y.), we found two heterozygous missense mutations in the *WNT1* gene. The *WNT1* gene encodes a signaling protein, which is among others involved in bone mineralization. So far, none of these mutations has been described in the literature. The online tools MutPred, SIFT and PolyPhen 2 classified these mutations as deleterious. Assuming a compound heterozygous state, the classification would be OI type XV, which correlates with the clinical diagnosis of OI type III for our patient.

### *Variant in the COL1A1 gene*

In five patients, we detected the variant c.104-441G>T (rs1800012) (E.L., E.S., L.R., S.Y., A.D.). Four patients were heterozygous for this transversion mutation, whereas one patient was homozygous (S.Y.). The frequency of this variant in the global population is 9%. It is associated with lower bone mineralization (1). The influence on the OI phenotype is most probably negligible.

### *Non-classified case*

For one of our patients (K.K.), no relevant mutation was detected with our NGS panel. So, this case remains unclassified for the moment. Mutation screening for the remaining autosomal recessive genes (Table 1) as a second round is in progress. This patient was clinically classified as OI type I, a moderate form of OI.

## DISCUSSION

Osteogenesis imperfecta is a disorder of bone formation that can be caused by different mutations in several genes (22-24). Thorough interdisciplinary diagnostics is necessary to explore the possible causes behind each individual case. Different pathogenic mechanisms may be involved, including aspects of bone metabolism such as bone formation, bone resorption, calcium, phosphorous and/or vitamin D homeostasis, defective collagen or defects in posttranslational processing of collagen, as well as errors in osteoblast differentiation and intracellular signaling (25). Primary and secondary causes of changes in bone structure have to be sorted out. Patients with severe bone deformities and multiple fractures often require combinations of therapies including medication with bisphosphonates, calcium and vitamin D, and extensive surgical treatments including telescope nails to shape, stabilize and strengthen femora and lower legs.

Molecular diagnosis of OI or severe osteoporosis causing genes does not only confirm the diagnosis. Greater awareness of the exact genetic profile of a patient supports the introduction of appropriate and timely treatments. In the cohort of patients reported here, a team of experienced clinicians diagnosed OI type III in most cases. In all but one patient, the genetic test result and the clinical diagnosis matched very well. There is only one out of 11 patients without a genetic diagnosis. Screening for mutation in other genes is in progress.

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SAŽETAK

# Molekularno-genetička analiza osteogenesis imperfecta u kliničkoj praksi

Annika Stubbe, Dragan Primorac,Wolfgang Höppner

*Osteogenesis imperfecta (OI) je obilježena prijelomima uz minimalnu ili odsutnu traumu i predstavlja kontinuum u rasponu od perinatalne smrtnosti, osobe s teškim skeletnim deformitetima do gotovo asimptomatskih osoba s niskom sklonošću prijelomima. Dijagnosticiranje OI je interdisciplinski zadatak koji se temelji na obiteljskoj i/ili bolesnikovoj povijesti prijeloma u kombinaciji sa znakovitim fizičkim nalazima. Radiografsko snimanje otkriva prijelome različite starosti i stadija zaraštanja, Wormove kosti i osteopeniju. Kako nema konačnog testa za OI, molekularno genetsko testiranje pomoću next generation sequencing (NGS) gena COL1A1 i COL1A2 te do 12 drugih gena bitno je za potvrdu genetske podloge. Stoga smo izradili NGS genski panel koji sadrži 12 gena uključenih u OI ili tešku osteoporozu. Prikazujemo rezultate dobivene u nizu od 11 očito sporadičnih mladih bolesnika s OI, svi potomci nezahvaćenih roditelja, koji su bili upućeni na ortopedsku kirurgiju u Specijalnoj bolnici sv. Katarina u Zaboku/Zagrebu. Deset od tih 11 bolesnika mogli smo genetski klasificirati. Sveukupno, uključena su bila tri gena u različitim postocima u našem nizu bolesnika: COL1A1 (63,6%), COL1A2 (18,18%) i WNT1 (9,09%).*

**Ključne riječi:** osteogenesis imperfecta; molekularna genetika - analiza