What is new in genetics and osteogenesis imperfecta classification?☆

Eugênia R. Valadares a,*, Túlio B. Carneiro a, Paula M. Santos b, Ana Cristina Oliveira b, Bernhard Zabel c

a Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil
b Faculdade de Odontologia, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil
c Pediatric Clinic, Freiburg University, Freiburg, Germany

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Abstract
Objective: Literature review of new genes related to osteogenesis imperfecta (OI) and update of its classification.
Sources: Literature review in the PubMed and OMIM databases, followed by selection of relevant references.
Summary of the findings: In 1979, Sillence et al. developed a classification of OI subtypes based on clinical features and disease severity: OI type I, mild, common, with blue sclera; OI type II, perinatal lethal form; OI type III, severe and progressively deforming, with normal sclera; and OI type IV, moderate severity with normal sclera. Approximately 90% of individuals with OI are heterozygous for mutations in the COL1A1 and COL1A2 genes, with dominant pattern of inheritance or sporadic mutations. After 2006, mutations were identified in the CRTAP, FKBP10, LEPRE1, PLOD2, PPIB, SERPINF1, SERPINF1, SP7, WNT1, BMP1, and TMEM38B genes, associated with recessive OI and mutation in the IFITM5 gene associated with dominant OI. Mutations in PLS3 were recently identified in families with osteoporosis and fractures, with X-linked inheritance pattern. In addition to the genetic complexity of the molecular basis of OI, extensive phenotypic variability resulting from individual loci has also been documented.
Conclusions: Considering the discovery of new genes and limited genotype-phenotype correlation, the use of next-generation sequencing tools has become useful in molecular studies of OI cases. The recommendation of the Nosology Group of the International Society of Skeletal Dysplasias is to maintain the classification of Sillence as the prototypical form, universally accepted to classify the degree of severity in OI, while maintaining it free from direct molecular reference.

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* Corresponding author.
E-mail: eugenia@medicina.ufmg.br, eugenivalvaladares@gmail.com (E.R. Valadares).

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Introduction

Osteogenesis imperfecta (OI) is a group of clinically and genetically heterogeneous diseases characterized by susceptibility to bone fractures, with variable degree of severity and presumed or proven defects in collagen type I biosynthesis. Other manifestations include dentinogenesis imperfecta, blue sclerae, and short stature, as well as hearing loss in adulthood. Clinical manifestations range from severe cases with perinatal lethality to asymptomatic individuals with mild predisposition to fractures, normal stature, and normal life.1

Overall, the incidence of the different types of OI is approximately 1 in 15,000-20,000 births and most cases are due to autosomal dominant inheritance with mutations in COL1A1 or COL1A2 genes, which encode the α1 (I) and α2 (I) chains of type I collagen.1

Type I collagen, the main structural protein of the extracellular matrix of bone, skin, and tendons, consists of two pro-α1 chains and one pro-α2 chain that interweave, forming a rigid triple helix. Each α chain contains N-(amino) and C-(carboxy) terminal propeptides and a central domain consisting of 338 repeats of Gly-XY, where X and Y exclude cysteine and tryptophan, and which often are, respectively, proline and hydroxyproline. Glycine, as the smallest amino acid, is the only residue that can occupy the axial position of the triple helix, so that any change in a glycine residue will result in the disruption of the helical structure.2,3

Mutations in COL1A1 and COL1A2 genes alter the structure or the amount of type I collagen, resulting in a skeletal phenotype that ranges from subclinical to lethal.1

These patients exhibit qualitative and quantitative abnormalities in type I collagen due to the dominant negative effect of the mutation, as the mutant pro-α chains are incorporated into the type I procollagen molecules that also contain normal pro-α chains. As a rule, when there is substitution of glycine in the α1 chain, the phenotype will depend on the position of the substitution: C-terminal substitutions result in severe disease phenotype, and N-terminal substitutions yield milder phenotypes.4,5 Residues with large lateral chains or charged residues are highly disruptive of the triple structure, regardless of where they are located. Different phenotypes have been found with the same mutation.5

In a consortium created in 2007 to study OI-causing mutations in type I collagen genes, 1,832 independent mutations were identified; 682 resulted in the substitution of glycine residues in the triple helix domain of the encoded protein, and 150 in splice sites.4 Based on clinical, radiographic, and skeletal findings, mode of inheritance, and molecular genetic analyses, new OI types have been identified since 2006 through exome sequencing. The present study aimed to review the classification of OI and to update new related genes. The PubMed and Online Mendelian Inheritance in Man (OMIM) databases were used.7

Silence Classification

Due to considerable phenotypic variability, Sillence et al.8,9 developed a classification of OI subtypes based on clinical features and disease severity (Table 1): OI type I, mild,
Table 1  
Classification of OI.

<table>
<thead>
<tr>
<th>Type</th>
<th>General manifestations</th>
<th>Specific manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>II- Perinatal lethal form, radiographically characterized by crumpled femora and beaded ribs.</td>
<td>Extreme bone fragility, perinatal death.</td>
<td>II-A: short and widened long bones with fractures, wide ribs with fractures.</td>
</tr>
<tr>
<td>III- Progressively deforming, with normal sclera.</td>
<td>Moderate to severe bone fragility, blue sclera in infancy.</td>
<td>Dentinogenesis imperfecta may be present.</td>
</tr>
<tr>
<td>IV- Autosomal dominant inheritance with normal sclera.</td>
<td>Bone fragility, moderate to severe deformity of the long bones and spinal column, white sclera, moderate to severe stunting.</td>
<td>IV-B: dentinogenesis imperfecta.</td>
</tr>
</tbody>
</table>

* Modified from Sillence et al.9

OI is a condition that affects connective tissue, impacting bone, cartilage, and other body tissues. It is characterized by bone fragility. The image mentions four main categories of osteogenesis imperfecta (OI) based on different inheritance patterns and severity:

1. **Autosomal dominant inheritance with blue sclera.**
   - General manifestations: Variable bone fragility, blue sclera, early deafness, mild stunting.
   - Specific manifestations: I-A: normal teeth.

2. **Perinatal lethal form, radiographically characterized by crumpled femora and beaded ribs.**
   - General manifestations: Extreme bone fragility, perinatal death.
   - Specific manifestations: II-A: short and widened long bones with fractures, wide ribs with fractures.

3. **Progressively deforming, with normal sclera.**
   - General manifestations: Moderate to severe bone fragility, blue sclera in infancy.
   - Specific manifestations: Dentinogenesis imperfecta may be present.

4. **Autosomal dominant inheritance with normal sclera.**
   - General manifestations: Bone fragility, moderate to severe deformity of the long bones and spinal column, white sclera, moderate to severe stunting.
   - Specific manifestations: IV-B: dentinogenesis imperfecta.

**Expanded Classification**

The molecular genetic classification of OI has been updated, showing that it is more complex than previously thought, with genetic and clinical variability.

**Common OI Types:**
- **OI type II:** This type is perinatal lethal and is characterized by blue sclera, severe bone fragility, and perinatal death. It is caused by mutations in the *LEPRE1* gene on chromosome 1p34.2.
- **OI type IV:** This type is autosomal recessive and is characterized by blue sclera and bone fragility. It is caused by mutations in the *SERPINH1* gene on chromosome 3p22.

**Expanded Classification:**
- **OI type VII (OMIM #610682):** This is a lethal autosomal recessive form of OI, caused by mutation in the *CRTAP* gene in homozygosity or compound heterozygosity in chromosome 3p22. It accounts for 2% to 3% of cases of lethal OI.
- **OI type IX (OMIM #259440):** This is an autosomal recessive form of OI corresponding to clinically severe types II/III of the Sillence classification.
- **OI type X (OMIM #613848):** This is an autosomal recessive form of the disease that can be caused by a homozygous mutation in the *SERPINH1* gene in chromosome 11q13.5.
- **OI type XI (OMIM #610968):** This is an autosomal recessive form of the disease caused by a homozygous mutation in the *FKBP10* gene in chromosome 17q21, also related to a chaperone defect.
- **OI type XII (OMIM #613849):** This is an autosomal recessive form, which can be caused by mutation in the *SP7* gene in chromosome 12q13.13. It is clinically characterized by recurrent fractures, mild bone deformities, generalized osteoporosis, delayed eruption of teeth, absence of dentinogenesis imperfecta, normal hearing, and white sclera.
Table 2  Expanded classification of OI.a

<table>
<thead>
<tr>
<th>Type of OI</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Genetic defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical Sillence Types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>AD</td>
<td>Mild</td>
<td>COL1A1</td>
</tr>
<tr>
<td></td>
<td>X-linked</td>
<td>Mild</td>
<td>PLS3</td>
</tr>
<tr>
<td>II</td>
<td>AD</td>
<td>Letal</td>
<td>COL1A1 or COL1A2</td>
</tr>
<tr>
<td>III</td>
<td>AD</td>
<td>Progressive deformity</td>
<td>COL1A1 or COL1A2</td>
</tr>
<tr>
<td>IV</td>
<td>AD</td>
<td>Moderate</td>
<td>COL1A1 or COL1A2</td>
</tr>
<tr>
<td>V</td>
<td>AD</td>
<td>Moderate, hypertrophic callus and ossification of the interosseous membrane</td>
<td>IFITM5</td>
</tr>
<tr>
<td>VI</td>
<td>AR</td>
<td>Moderate to severe</td>
<td>SERPINF1</td>
</tr>
<tr>
<td>VII</td>
<td>AR</td>
<td>Severe to lethal</td>
<td>CRTAP</td>
</tr>
<tr>
<td>VIII</td>
<td>AR</td>
<td>Severe to lethal</td>
<td>LEPRE1</td>
</tr>
<tr>
<td>IX</td>
<td>AR</td>
<td>Severe to lethal</td>
<td>PPIB</td>
</tr>
<tr>
<td>X</td>
<td>AR</td>
<td>Severe</td>
<td>SERPINH1</td>
</tr>
<tr>
<td>XI</td>
<td>AR</td>
<td>Progressive deformity, contractures</td>
<td>FKBP10</td>
</tr>
<tr>
<td>XII</td>
<td>AR</td>
<td>Moderate</td>
<td>SP7</td>
</tr>
<tr>
<td>XIII</td>
<td>AR</td>
<td>Severe</td>
<td>BMP1</td>
</tr>
<tr>
<td>XIV</td>
<td>AR</td>
<td>Variable severity</td>
<td>TMEM38B</td>
</tr>
<tr>
<td>XV</td>
<td>AR</td>
<td>Variable severity</td>
<td>WNT1</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Early-onset osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive.

a Adapted from Forlino et al.1

OI type XIII (OMIM #614856) was described as caused by a homozygous mutation in the gene BMP1 in chromosome 8p21.15,26

Shaheen et al.27 described OI type XIV (OMIM #615066), an autosomal recessive form characterized by varying degrees of severity with multiple fractures and osteopenia, with normal dentition, sclera, and hearing. Fractures occur prenatally or at approximately 6 years of age. It is caused by a homozygous mutation in the gene TMEM38B in chromosome 9q31.

OI type XV (OMIM #615220) has been designated based on the identification of mutations in WNT1.18-20 Keupp et al.30 reported that WNT1 hypofunctional alleles result in phenotypes with low bone mass in humans. They verified that mutations in the recessive inherited gene lead to phenotypes of varying severity, ranging from mild to progressively deforming, which can occasionally lead to early infant death. They also detected families that had early osteoporosis with the autosomal dominant pattern of inheritance, with a heterozygous mutation in WNT1. The recessive forms of OI with moderate to lethal phenotypes are caused by defects in genes whose products interact with collagen type I. Most recessive cases have null mutations in genes encoding proteins involved in prolyl 3-hydroxylation of collagen (CRTAP, LEPRE1, and PPIB), or in those responsible for the correct helical folding (FKBP10 and SERPINH1). Types VII, VIII, and IX are caused by defects in 3-hydroxylation.1 The genotype-phenotype correlation in recessive forms has been suggested.31

In 2013, PLS3 mutations were identified in families with osteoporosis and fractures manifesting in childhood, with an X-linked pattern of inheritance.31

Table 2 summarizes the classification based on the involved genes.

In 2010, van Dijk et al.33 proposed a revised classification of OI, mentioning the causative gene and the corresponding clinical picture only for types I to VI. Types VII and VIII were excluded, as those types were added by genetic criteria, although their clinical and radiological findings were indistinguishable from those in types II to IV. The proposed classification leaves room for new genes discovered as the cause of OI until the full extent of heterogeneity is known.34

**OI Classification by the International Society of Skeletal Dysplasias**

Due to the high genetic complexity of the molecular basis of OI and the extensive phenotypic variability resulting from individual loci described in recent years, it seemed impossible to maintain correlations between Sillence types and their molecular basis. But the proliferation of OI types to reflect each gene separately, supported by some, has become more confusing than useful in clinical practice. For these reasons, in 2009 the Nosology Group of the International Society of Skeletal Dysplasias recommended maintaining the classification of Sillence as the prototypical and universally accepted form to classify the degree of OI severity, and freeing it from direct molecular reference.35 Thus, as shown in Table 3, OI was grouped into five clinical categories, and the several genes that can cause OI were listed separately. In the present study, the genes IFITM5, SERPINF1, BMP1, WNT1, TMEM38B, and PLS3 were added to the original table, as they were discovered after its publication.
### Table 3

<table>
<thead>
<tr>
<th>Osteogenesis Imperfecta</th>
<th>Inheritance</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondeforming osteogenesis imperfecta (type I)</td>
<td>AD</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td></td>
<td>X-linked</td>
<td>PLS3</td>
</tr>
<tr>
<td>Perinatal lethal (type II)</td>
<td>AD, AR</td>
<td>COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, BMP1</td>
</tr>
<tr>
<td>Progressively deforming (type III)</td>
<td>AD, AR</td>
<td>COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SERPINF1, WNT1</td>
</tr>
<tr>
<td>Moderate (type IV)</td>
<td>AD, AR</td>
<td>COL1A1, COL1A2, CRTAP, FKBP10, SP7, SERPINF1, WNT1, TMEM33B</td>
</tr>
<tr>
<td>With calcification of the interosseous membrane and/or hypertrophic callus (type V)</td>
<td>AD</td>
<td>IFITM5</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive.

* Reference:**