Molecular genetics of osteogenesis imperfecta

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Abstract. Osteogenesis imperfecta (OI) or imperfect formation of bone, is a disorder that affects the bone genetically. The range of clinical presentation of osteogenesis imperfecta lies widely from first trimester intrauterine day to later in life. Depends on the clinical features, it’s hard to distinguish OI fractures from other causes of fractures, like genetic, non-genetic, and non-accidental injury. OI is a group of genetically heterogeneous bone-related genetic disorders, characterized, by bone fragility, frequent fractures, deformities of the spine and limbs, with just minimal trauma, this disease is also known as “brittle bone disease”. Many recent studies identified molecular genetic defects underlying Osteogenesis Imperfecta. Osteogenesis imperfecta has a prevalence of 1 in 15-20,000 newborns. Gene signaling events of osteogenesis or collagenases pathobiology will give use another approach for the treatment of Osteogenesis Imperfecta in recent days. Osteogenesis imperfecta is a disorder related to the bone with a broad description of characteristics. Most of the individuals with Osteogenesis Imperfecta are caused by correlating gene mutation in collagenogenesis encoding gene, which is COLIA1 and COL1A2, but in recent years, many other genetic causes have been known as the lead of this disease, such as mutation of such genes, LEPRE, SERPIN, WNT, BMP, IFITM. These genes are known as the correlated gene in the collagenogenesis and the other correlates to bone formation and maturation.

1. Introduction
Osteogenesis imperfecta (OI) or imperfect formation of bone, is a disorder that affects the bone genetically. The range of clinical presentation of osteogenesis imperfecta lies widely from first trimester intrauterine day to later in life. Depends on the clinical features, it’s hard to distinguish OI fractures from other causes of fractures, like a genetic, non-genetic, and non-accidental injury. In this paper, we will discuss the strategies for the assessment and examines that would help to recognized causes of bone deformity and fractures of bone and how to treat them genetically [1].
2. Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a group of genetically heterogeneous bone-related genetic disorders, characterized by bone fragility, frequent fractures, deformities of the spine and limbs, with just minimal trauma, this disease also known for “brittle bone disease”. The current classification of osteogenesis imperfecta (OI) types I–V with autosomal dominant (AD) genetic inheritance and eight rare forms OI types VI–XIII with recessive genetic inheritance. Clinical features of OI may vary from low to a high amount of fractures to advanced bone deformation and natal death, blue sclera, loose joints, hearing problem, short height, breathing problems, and sometimes with a problem with teeth (Dentinogenesis Imperfecta). Most of the cases of Osteogenesis Imperfecta lies in the types I, II, III, and IV, which are dominant mutations in one of these genes, the collagenogenesis coding gene, COL1A1, and COL1A2 [2-5]. Typically, mutations in COL1A1 and COL1A2 genes lead to the defective formation or quantity of type I collagen, the principal matrix in connective tissues of bones, ligaments, and sclerae [6].

3. Clinical Features

The clinical hallmark of OI is a low bone mass that causes bone fragility, easy fracturing, and growth impairment, nor deformity in bone and short height. Other features may include blue sclerae, dentinogenesis imperfecta, and hearing loss.[1] The incidence of OI that can be identified at birth is 1 case per 15,000 to 20,000 newborns. Studies in Europe and the US (United States) found that 3 to 7 cases per 100,000 newborns have osteogenesis imperfecta.8 The prevalence of lethal Osteogenesis Imperfecta in the Netherlands was reported to be 5 cases per 100,000 newborns [7].

4. Classification and clinical features

Osteogenesis Imperfecta type I, autosomal dominant genetic inheritance. Clinically has fractures with a wide range of limb deformity (from light to heavy), blue sclerae, normal height, some with hearing loss and abnormality in dentin or dentinogenesis imperfecta. The ultrasound finds long-bone bowing and fractures very rarely. The specific mutated gene associated with this type is COL1A1 and COL1A2. First ultrasound detection in 20 weeks [8-9].

Osteogenesis Imperfecta type II, Autosomal dominant genetic inheritance, in clinical feature, it has under the mineralized skull, micromelic bones, x-ray photo show “beaded” ribs, deformity in bone, platyspondily. The ultrasound finds under mineralization, wide, wrinkled, and curved limbs, slim beaded ribs, fractures of long bones, angulation of the long bones or bending of bone, with usual showing hands, deform calvarium. The specific mutated gene associated with this type is COL1A1 and COL1A2. First ultrasound detection in 14 weeks [8-9].

Osteogenesis Imperfecta Type III has autosomal dominant genetic inheritance, clinically has a malformation of limbs, different scleral hue, very short height, and abnormalities of dentin formation. The ultrasound finds lean ribs, curt limbs under the mineralized skull, some perform with a fracture in the skull, in 16-18 weeks long-bone extent far away from normal. The specific mutated gene associated with this type is COL1A1 and COL1A2. First ultrasound detection in 18 weeks [8-9].

Osteogenesis Imperfecta Type IV, has autosomal dominant genetic inheritance, clinically doesn’t have blue sclerae, limb deformity mild to moderate limb sometimes occur with fracture, short variable height, dentinogenesis imperfecta and some loss in hearing. The ultrasound rarely finds long bone bowing and/or fracture. A specific mutated gene associated with this type is COL1A1 and COL1A2. First ultrasound detection in 20 weeks [8-9].

Osteogenesis Imperfecta type V has autosomal dominant genetic inheritance, OI type V has similar characteristics with OI type IV, with interosseous membrane calcification of fore-arm, dislocation radial head, and formation of hyperplastic callus [8-9].

Osteogenesis Imperfecta Type VI, clinically have similarity with type IV Osteogenesis imperfecta, but with more fractures and vertebral pressure fractures without dentinogenesis imperfecta [8-9].

Osteogenesis Imperfecta type VII, clinical findings show congenital fractures, colored sclerae (blue), hip deformation, leg deformation, and osteopenia. A specific mutated gene associated with this type is CRTAP. This type of OI has an autosomal recessive genetic inheritance [8-9].
5. Molecular aspects of osteogenesis imperfecta

Mechanism of OI is a defect in type I collagen genesis and defects in formation and mineralization of bone. Collagen type I defects contain disruption in synthesis collagen and processing of collagen, disruption of structural and quantitative collagen, disruption of collagen processing, disruption in collagen post-translational change, and disruption in collagen chaperones and crosslinking [10-11].

Type I collagen is a triple-helical molecule consists 2 chains of two proα1 and one proα2, encounter post-translational change (hydroxylation and glocalization), synthesized to procollagen (propeptide and carboxyl), and undergo proteolytic cleaved by protease ADAMTS2 and BMP1. The collagen chain’s order is Gly-Xaa-Yaa, with glycin each every 2 chains, and X and Y is an amino acid. through the α1-chain, some area singles out to bind with another collagen with MLBR (major ligand-binding region) [10,11].

![Figure 1. Structure of COL1A1](image)

Although there are 20 different recessive genes connected to OI pathology, about 70%–90% of patients with OI harbor dominant pathogenic variants in the COL1A1 (OMIM accession number 120150) and COL1A2 (OMIM accession number 120160) genes. These genes code for collagen type I α1 and α2 chains, respectively. Collagen type I is an essential structural protein and is the most abundant structural protein in the human body. Collagen chains consist of Gly‐X‐Y triplet motifs where every third position is occupied with glycine. The importance of collagen type I is evidenced by its high conservation among vertebrates. Collagen type I naturally lacks variation on its termini, especially in the C-terminal domain. These termini are highly conserved, as they have vital functions, such as collagen assembly, transport, and signaling [10].

The first process of collagenogenesis is a translation of the pro-alpha chain and modification post-translational of collagen pro-α1 and collagen pro-α2 chains. Osteoblast, fibroblast, tenositis, and triple helix secrete major protein parts. Transcript of COL1A1 and COL1A2 gene, translated to Endoplasmic Reticulum, undergo modification translation of GLY-Xaa-Yaa. Helical proline X, hydroxylated by C4 (P4H1). Helical proline Y, hydroxylated P3H1. Lysin residue is hydroxylated by lysyl hydroxylase (LH1 and LH2). Mutation of COL1A1 and COL1A2 causes a decrease of normal type 1 collagen quantitatively, or collagen with a structural defect. A common mutation is succession glycin with residue and some defect structure [11].

Formation of triple helix complex of collagen chain comprises 2 of pro-α1 chains and 1 of a pro-α2 chain. Collagen processing defect, extracellular cleavage from propeptide need to spontaneous assembly collagen and fibril and fiber formation in ECM. BMP1 and ADAMTS are encoding genes that important for these processes. Defects in BMP1, cause the presence of PC-collagen in the extracellular matrix, which matures collagen with C-propeptide attached in the chain. These mutations in dominant mutations that cause mild OI with normal bone density [11].

Defect in collagen post-translational modification. Patients with recessive inheritance of OI defect in fundamental post-translational modification and appropriate folding type 1 collagen. CRTAP and P3H1
are encoding genes that important for these processes. Alteration in any genes which encode this protein is associated with OI [8].

![Figure 2. Synthesis and Processing type I Collagen [8]](image)

Defects or alterations in bone formation and mineralization include damage or weaken in bone mineralization and defects in osteoblast differentiation and function. Some OI is caused by a disruption in collagen pathway, alteration of gen which mineralized and differentiates of osteoblast [8].

![Figure 3. Defects in Bone Formation and Mineralization [13]](image)

Another mechanism that causes OI, caused by a disruption in bone formation and mineralization. Figure 3, Bone formation process is a process where osteoblast release a matrix component, type I collagen into an extracellular matrix component until osteoid or unmineralized bone matrix then becomes mineralized. Also, cytokine, released by osteoblast and osteocytes, arrange bone resorption—one of the cytokines which arrange bone resorption RANKL, also known as TNFSF11 and OPG. Osteoclast production happens, because there are binding of RANKL to RANK; or TNFRSF11A agitate their maturation become osteoclast. Conversely, OPG, is the protein generated by osteoblast, acts as a decoy receptor for RANKL, as a competitor to obstruct the binding of RANKL to RANK, so to reduce
osteoclastogenesis and reduce bone resorption. Osteoblasts which stacked in the mineralized bone matrix and differentiated into osteocytes, and generate sclerostin, a WNT pathway inhibitor. WNT (wingless-type integration) pathway stimulates osteoblast activity to stimulate bone formation. WNT is a family of signaling molecules that includes 19 members in humans. The signal is transmitted to a complex receptor such as frizzled and LRP5 or 6. Their signal is transmitted to undergo a canonical pathway. WNT1 is a group of WNT gene family, interacts with receptors LRP5 or 6 on osteoblast precursor cells, and then stimulates the transcription of genes for osteoblast differentiation [11,13].

In the Golgi, a protease which embroiled in regulated proteolysis is endopeptidase S2P, an old astrocyte specifically induced substance (OASIS). In times of ER stress, OASIS is transmitted from the endoplasmic reticulum (ER) membrane. PEDF “Pigment epithelium-derived factor” and BRIL is a multifunctional protein embroiled in the mineralization of the bone. Patients with a mutation in a gene connected to osteogenesis imperfecta show unwanted transfer signals between the two proteins. Osteogenesis imperfecta is associated with a mutation in any genes which encode this protein, including InsP 3 R, OASIS-N, MALEP, S40L, TRIC-B, and VEGF [8].

Most individuals with Osteogenesis Imperfecta, may have mutations in one of two collagenogenesis encoding genes, between COL1A1 or COL1A2. Another significant number of individual diagnoses with OI which does not have a mutation in one of the collagenogenesis encoding genes, this individuals undergo recessive mutations and undergo mutation in protein-encoding genes which involved in the process of collagenogenesis, and collagen post-translational processing or modification. These encoding genes including, CRTAP, LEPRE1, PPIB, and BMP1, and for pro-collagen formation, a mutation in genes SERPINH1 and FKBPI0 10 osteoblast differentiation SP7/OSX [4].

6. Conclusion

Osteogenesis imperfecta is a disorder related to the bone with a broad description of characteristics. Most of the individuals with Osteogenesis Imperfecta are caused by correlating gene mutation in collagenogenesis encoding gene, which is COL1A1 and COL1A2, but in recent years, many other genetic causes have been known as the lead of this disease, such as mutation of such genes, LEPRE, SERPIN, WNT, BMP, IFITM. These genes are known as the correlated gene in the collagenogenesis, and the other correlates to bone formation and maturation.

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