Valenti MT et al. Deform Bone Muscles 2018(1): 06-15.
https://doi.org/10.33513/DBMS/1801-04

OCIMUM

Deformities in Bones and Muscles Journal

Review Article

Osteogenesis Imperfecta: A Heterogeneous Heritable Disease

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Received: 26 November 2018
Accepted: 08 December 2018
Version of Record Online: 04 January 2019

Citation

Deiana M, Malerba G, Dalle Carbonare L, Mottes M, Valenti MT (2018) Osteogenesis Imperfecta: A Heterogeneous Heritable Disease. Deform Bone Muscles 2018(1): 06-15.

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Abstract

Bone is a dynamic organ, able to replace old or disrupted tissue through a remodelling process. It contains a relatively small number of cells (osteoblasts, osteocytes, osteoclasts and Mesenchymal Stem Cells (MSCs)) entrenched in a matrix. Perturbation or disruption of the complex molecular pathways controlling MSC proliferation and osteogenic commitment may be determined by mutations affecting key genes in bone development. Osteogenesis Imperfecta (OI) also known as brittle bone disease is a genetic pathology in which bones do not form properly and therefore are fragile and break easily. OI is a heterogeneous congenital heritable disease that mainly affects connective tissues. Nowadays we number 18 types of OI, characterized by various modes of inheritance: autosomal dominant, recessive and X-linked.

Keywords

Bone; Mesenchymal Stem Cells; Osteogenesis Imperfecta

Bone Ossification in the Foetus Childhood and Adolescence

Two osteogenic process characterize skeletal development: intramembranous and endochondral ossifications. Ossification is a complex process orchestrated by Mesenchymal Stem Cells (MSCs) able to differentiate either into osteoblasts or chondrocytes [1]. In intramembranous ossification MSCs direct differentiate into osteoblasts and usually occurs in the flat bones as skull, jaw and in the sub-periosteum areas of long bones. Early osteoblasts occurs in cluster called ossification centre, although osteoblasts will be spreaded out by during formation of bone [1]. Osteoblasts secrete osteoid, an uncalcified matrix, which within a few days calcifies trough a mineral salts deposition, thereby entrapping the osteoblasts in the matrix. Entrapped osteoblasts will become osteocytes [2]. As osteoblasts-osteocytes transformation, also osteogenic cells present in the surrounding connective tissue may differentiate into new osteoblasts. Unmineralized bone matrix secreted around the capillaries became a trabecular matrix, while osteoblasts on the surface of the spongy bone form the periosteum. The periosteum represents the protective surface layer above trabecular bone [3,4]. Intramembranous ossification that begins during foetal development prosecutes until adolescence. At birth, the skull and clavicles bones are not fully ossified [4]. Bones plasticity allows skull and shoulders to deform during passage through the birth canal.

In endochondral ossification, process that occurs in long bones formation, mesenchymal stem cells differentiate into chondrocytes and secrete a cartilaginous matrix. Cartilage scaffolds are then replaced by bone, increasing the ability to counteract the compression. For example, six-eight weeks after conception, mesenchymal cells differentiate into chondrocytes which form the cartilaginous skeletal precursor of a long bone [5]. The canonical bone development model involves the differentiation of mesenchymal stem cells into a specific cell lineage fate, depending on the time and signalling [6]. As more matrix is produced, more chondrocytes grow in size. Matrix calcification inhibits nutrients reaching to the chondrocytes. During cartilage grows, capillaries penetrate it, starting the transformation of perichondrium into the bone-producing periosteum. Here, osteoblasts form a periosteal compact bone frame that surround the diaphysis cartilage [7]. From the third month of foetal life, in the periosteal collar bone development creates the primary ossification centre, where ossification begins. Chondrocytes and cartilage continue to grow at the ends of the bone, forming the future epiphyses [4]. While length increases, bone is replacing cartilage in the diaphysis. When the foetal skeleton is fully formed, cartilage remains only at the joint surface and between the diaphysis and epiphysis [4]. After birth, matrix mineralization, chondrocytes' death, invasion of blood vessels from the periosteum, and osteoblasts maturation occurs in the epiphyseal regions, and all these activities centres is referred to as a secondary ossification centre.

Childhood and adolescence are characterized by a progressive growing and by enhanced bone mass. At birth the skeleton weights about 75-90 g; it reaches 2400-3000 g in the young adult [8]. The epiphyseal plate represents the growth area in a long bone. It is a layer of hyaline cartilage where ossification occurs in immature bones. The reserve zone is the region closest to the epiphyseal end of the plate and contains small chondrocytes within the matrix. These cells do not participate in bone growth but secure the epiphyseal plate to the osseous tissue of the epiphysis. The proliferative zone is the next layer towards the diaphysis and contains stacks of slightly larger chondrocytes. It makes new chondrocytes (via mitosis) in order to replace those that die at the diaphyseal end of the plate. Chondrocytes in the next layer, the zone of maturation and hypertrophy, are older and larger than those in the proliferative zone; the more mature cells are located closer to the diaphyseal end of the plate [8]. Bone longitudinal growth is a result of cellular division in the proliferative zone and cellular maturation within the zone of maturation and hypertrophy, respectively. In calcified matrix, the zone closest to the diaphysis, most chondrocytes are dead. Capillaries and osteoblasts from the diaphysis penetrate this zone; osteoblasts secrete bone tissue on the remaining calcified cartilage. Thus, the zone of calcified matrix connects the epiphyseal plate to the diaphysis. A bone grows in length when osseous tissue is added to the diaphysis. The growth rate is controlled by hormones; bones continue to grow in length until early adulthood. Bone growth includes also increasing in diameter, this can continue even after longitudinal growth ceases and it is called appositional growth. Osteoclasts resorb old bone that lines the medullary cavity, while osteoblasts, via intramembranous ossification, produce new bone tissue beneath the periosteum. The canonical endochondral ossification leads to the apoptosis of hypertrophic chondrocytes and the vascular invasion that induce the osteoclast precursors to remove cartilage, while the osteoblast begin to form new bone [6]. Recently have been reported the ability of chondrocyte to transdifferentiate into osteoblast during endochondral ossification process. Three majors mechanistically different transdifferentiation process has been described. The first two process involve an intermediate transdifferentiation, while the third model direct transdifferentiation occur [6]. The chondrocyte switch into Osteogenic Precursor (OP) suggests that in the growth plate immature chondrocytes may differentiate into a transient osteogenic precursor in the metaphysis [9]. In the second intermediate transdifferentiation, chondrocytes dedifferentiate into immature chondrocytes and to redifferentiate into osteogenic lineage. It has been described during embryonic and post-natal development [9]. The third model, described as direct transdifferentiation, is the method by which post-natal secondary ossification occurs. Mature, hypertrophic and not apoptotic chondrocytes differentiate directly into osteoblasts and then into osteocytes [6].

Osteogenesis Imperfecta: History

Perturbation or disruption of the molecular pathways controlling MSC proliferation and osteogenic commitment may be due to mutations in key genes in bone development. Osteogenesis Imperfecta (OI) also known as brittle bone disease is a genetic pathology in which bones do not form properly and therefore are fragile and break easily [10]. It is a heterogeneous heritable disease that mainly affects connective tissues. The estimated incidence is approximately 1 per 20,000 live births [9]. The various genetic mutations that cause OI in 85% of cases affect type I collagen- one of the critical components of bone matrix, either quantitatively or qualitatively [11]. The first studies on OI were done in 1788 by Olof Jakob Ekman; it can actually be considered a very ancient pathology. During archaeological studies some Egyptian mummies were found; the description of their skull, teeth and flat bones abnormalities suggests that they were affected by OI [12]. In 1979 Sillence et al., described OI as a heterogeneous disease and, for the first time, they proposed a classification of at least four distinct types [13].

Phenotypes of Osteogenesis Imperfect

The hallmarks of the brittle bone dysplasia Osteogenesis Imperfecta are skeletal deformities and bone fragility that causes low bone mass and bone fractures [13]. The severity of the disease can range from mild to lethally severe. Frequent and multiple fractures typically lead to bone deformities and short stature. In the mildest forms, fractures tend to decrease in the adults, but postpartum or in menopause may re-occurs [14]. Since type I collagen is such an important structural protein in many connective tissues, people with OI may also experience fragile skin, weak muscles, loose joints, easy bruising, frequent nosebleeds, brittle teeth, blue sclerae, and hearing loss. The clinical features can be divided into skeletal and extra-skeletal manifestations. Skeletal features involve excess or atypical fractures, short stature, scoliosis, and basilar skull deformities, while extra-skeletal symptoms include hearing loss, it is found in 50% of adults by age 50 and in 5% of children with OI [15]. Dentinogenesis Imperfecta (DI), consist in small deformed teeth, which present opalescent and opaque dentin. Malocclusion and DI, are the main dental abnormalities which may occur. The phenotype is variable also within the same patient, with some teeth appearing normal and others being affected [16]. The sclerae may be blue or grey, colour can be stable of became less dark. Blue sclerae it is characteristic of OI type I and of mildest forms [17]. Connective tissue abnormalities may result in dislocation of head of the radius and the joint. 36% of patients that manifest hypercalciuria, may result in renal calculi [18,19]. Cardiovascular complications leads to aortic root dilatation and mitral valve prolapse. Also, neurological manifestations have been reported and include macrocephaly, hydrocephalus, basilar invagination and cervical spine kyphosis. Hearing impairment is a common symptom in OI, from 39% to 57.9% [12]. Its prevalence increases over the time, it usually manifests between the second and fourth decade, and it is progressive [20]. Patients with OI are characterized by low areal Bone Mineral Density (aBMD), associated to lower bone size and lower volumetric BMD [21]. Histomorphometric evaluation shows increased cortical porosity, low cortical width and trabecular bone volume reduction [22,23]. However, bone may appear hypermineralized with smaller and abundant mineral crystals, process associated with lower mechanical strength [24]. In Figure 1 are reported some examples of AD OI types (A, B, C), AR that affects bone mineralization (D, E) and also few cases of abnormal collagen post-translational modification (E, F).

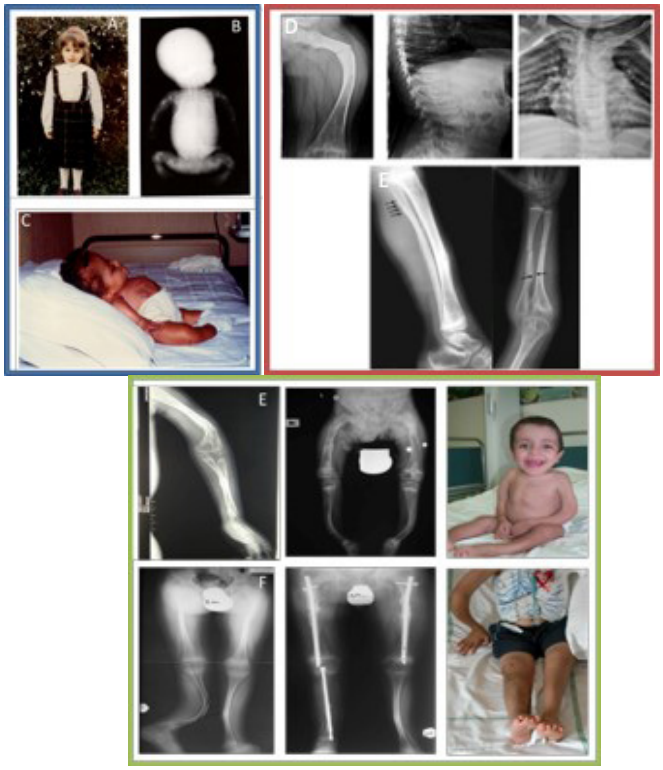

Figure 1: Clinical features associated with Osteogenesis Imperfecta. In a blue box some examples of dominant forms of OI, part A type I OI, part B a radiographic images showing severe curvature of the legs in type II OI, and part c a picture of type III OI patients. In a red box, part D illustration the radiograph of limbs in type VI OI, part E the radiographs of the patient's limbs showing fractures and interosseous membrane calcifications development as well as the initial evidence of periosteal calcification (arrows) Radial head dislocation is visible on the forearm anteroposterior view patients with Osteogenesis Imperfecta. In a green box part F a patient at 5 years affected by type VII OI; the patient has a normal head, white sclerae, small thorax and shortening of the proximal segment of the upper and lower extremities. In the left, detail of arm and legs showing osteopenia, undertubulation and severe deformities, consistent with a severe deforming form of Osteogenesis Imperfecta. Part F patient affected by type VIII OI, radiograph show bowed limbs and severe osteopenia and undertubulated long bones [25-28].

Genetic Classification and Pathophysiology of OI

Mutations in genes coding for the α1 and α2 chains of the heterotrimeric type I collagen [(1)2 2(1)] were associated to Osteogenesis imperfecta in 1980 [15]. Type I collagen is the most abundant protein of bone, skin, and tendon; in teeth and bone it plays a fundamental role in the mineralization process. COL1A1 and COL1A2 mutations are the most common defects (85% of OI cases) transmitted as autosomal inheritance. COL1A1 loss-of-function mutations cause a quantitative loss of in α1(I) chains of type I collagen trimers; they typically generate a mild form of OI (type I) [15]. Quantitative defects are associated with the milder osteogenesis imperfecta type I. Other mutations in COL1A1 or COL1A2, such as glycine substitutions in the Gly-X-Y repeat, lead to structural defects of the collagen triple helix. They exert a dominant negative effect on the normal collagen chains upon trimers formation, and result in either moderate, severe or lethal OI. Structural collagen defects can cause moderate and progressive deforming type IV and type III, respectively, as well as lethal type II [29].

In the past decade, a wide variety of genes encoding proteins involved in type I collagen synthesis, processing, secretion and post-translational modification, respectively, as well as in genes coding for proteins that regulate the differentiation and activity of bone-forming cells have been shown to cause Osteogenesis Imperfecta [30]. In 2006 CTRAP, was identified as the first gene causing recessively inherited OI, opening the way to an exciting new information about the genetics and mechanism of this bone dysplasia.

OI classification initially included four phenotypes (Sillence classification [31]): type I, or the non-deforming type, autosomal dominant mild form, characterized by blue sclerae, type II, with autosomal recessive inheritance the most severe form (lethal perinatally) an type III, autosomal recessive inheritance severe form, that manifests progressive deformity and type IV autosomal dominant inheritance form with moderate severity [14]. Clinical manifestation of COL1A1 and COL1A2 mutations are reported in box1 [32] (Table 1).

OI type	Phenotype
1/I	Mild, nondeforming and lethal forms
2/II, VII, VIII, IX, XII	Severe, seen as perinatal
3/III, VII, VIII, IX, XI, X, VI, XV	Moderate to severe, progressively deforming
4/IV, VII, XI, XIII, VI, XV, XIV	Moderate
5/V	Moderate with calcification of the interosseous membrane and/or hypertrophic callus

Table 1: The International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton 2009.

The discovery of new OI associated genes has led to two new approaches to classification: 1) a more clinically based approach in which the new recessive types are included under the Sillence-types, 2) a genetic–functional approach in which the Sillence types I–IV are reserved for mutations in COL1A1 or COL1A2 and new genes are given additional type numbers based on the mutation without clinical correlation (Table 2)

Mutaded gene	Encoded protein	Inheritance	Localization	Severity	OI type
Impairment of collagen synthesis and structure					
COL1A1	Collagen α1	AD	matrix structural component	Mild to lethal	I,II,III or IV
COL1A2	Collagen α2	AD	matrix structural component	Moderate to lethal	I,II,III or IV
Compromised bone mineralization					
IFITM5	BRIL	AD	bone-restricted interferon-induced transmembrane like protein	variable severity	V
SERPINF1	PEDF	AR	collagen-binding protein/pigment epithelium derived factor	Moderate to severe	VI
Abnormal collagen post-translational modification					
CTRP	CTRAP	AR	endoplasmic reticulum	Severe to lethal	VII
P3H1 (LEPRE1)	P3H1	AR	endoplasmic reticulum	Severe to lethal	VIII
PPIB	PPIase B	AR	endoplasmic reticulum	Moderate to severe	IX
Compromised collagen processing and crosslinking					
SERPINH1	HSP47	AR	endoplasmic reticulum-golgi	Severe to lethal	X
FKBP10	FKBP65	AR	endoplasmic reticulum	Moderate to severe	XI
PLOD2	LH2	AR	endoplasmic reticulum	Moderate to severe	no type
BMP1	BMP1	AR	endoplasmic reticulum	Moderate to severe	XII
Alternate osteoblast differentiation and function					
SP7	Transcription factor SP7/ osterix	AR	nucleus	Mild to moderate	XIII
TMEM38B	TRIC-B	AR	cation channel	Moderate to severe	XIV
WNT1	WNT1	AR/AD	secreted signal molecule	Moderate to severe	XV
CREB3L1	OASIS	AR	endoplasmic reticulum-golgi	Severe	XVI
SPARC	SPARC/osteonectin	AR	matrix	Moderate to severe	XVII
MBTPS2	S2P	XLR	endoplasmic reticulum-golgi	Moderate to severe	XVIII

Table 2: Genetic classification of OI.

[31]. In 2009, the International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton (INCDS) proposed a new classification, divided in five different groups based on phenotypical traits. The individual OI disorders still retain their Roman identification number and in addition they are classified with an Arabic numeral that indicates the phenotypic description, see table 1. The large number of causative genes discovered since 2006 has complicated the classic classification of the disease, and, although a new genetic classification system is widely used, it is still debated. In OI patients have been described a huge defects in proteins with very different functions, ranging from structural to enzymatic and from intracellular transport to chaperones [10]. Nowadays we number 18 different types of OI, distinguished by autosomal dominant, recessive and X-linked inheritance.

Type I

Caused to COL1A1 or COL1A2 mutation. The clinical manifestations include osteopenia, vertebral fractures, usually not deforming but can lead to scoliosis. Fractures are mostly during childhood and it is associated with extraskeletal defects as blue sclera, presenile deafness, and aortic regurgitation. At X-ray skull and spinal cord shows thin cortices [11].

Type II

Fractures manifests even before birth and affects rib, long bone, and skeletal fractures. Due to respiratory insufficiency, central nervous system malformations, and hemorrhages death can occur. Other phenotypical traits manifested are blue sclera and dentinogenesis imperfecta. X-ray showed undermineralization, severely deformed extremities [11].

Type III

Fractures can start in utero or at birth, bringing to a progressive deformity and scoliosis. At birth they present triangular facies, blue sclera and manifests dentinogenesis imperfecta. Are characterized by short stature, severe long bone deformities, fractures, and possibility to develope respiratory hypoplasia. Frequently manifests hearing loss [11].

Type IV

At birth they may present progressive deformity. Typical traits of type IV concerns greyish or white sclera, dentinogenesis imperfecta, short stature, may have long bone bowing, scoliosis, and joint laxity, although phenotypes are significantly variable [11].

Type V

They present fractures and hypertrophic calluses that is associated with progressive deformity. Calcification of the interosseous membranes of the forearm can lead to decreased hand mobility and radial head dislocation, moreover present irregular mesh-like bone. X-ray investigation shows macrocephaly and Wormian bones, scoliosis [11].

Type VI

Phenotype appear from moderate-to-severe deformities. They may have blue sclera. At birth are healthy with subsequent progressively severe deformities. It is characterized by unmineralized bone and "fishscale" pattern on iliac crest biopsies. Back reveals scoliosis and compression fractures [11].

Type VII

Phenotype of type VII OI (CRTAP deficiency) overlaps Sillence types II and III but has distinctive features. Causes severe to lethal osteochondrodysplasia with rhizomelia, neonatal fractures, broad undertubulated long bones, frail ribs. Sclerae are white or light grey. Severe growth deficiency and "popcorn" calcifications of epiphyses are seen in individuals who survive into childhood, which are also observed in about half of type III OI patients [11].

Type VIII

They manifest progressive deformities and short stature. Back reveals severe scoliosis and could be similar to OI Type II/III. Individuals with types VII and VIII OI exhibit a similar phenotype due to the mutual stabilization between CRTAP and P3H1 [11].

Type IX

Blue sclera and severe deformities are the common traits. They may have short stature. Back reveals kyphoscoliosis and skeletal features similar to OI Type II/III/IV [11].

Type X

It is characterized by severe bone deformities and multiple fractures, generalized osteopenia, dentinogenesis imperfecta, and blue sclera. They may have renal stones [11].

Type XI

Severe deformities are seen. Patients with type OI type XI have severe progressive deformation and may have joint contractures, dentinogenesis is normal [11].

Type XII

They have recurrent fractures and mild bone deformities, delayed tooth eruption, generalized osteoporosis, delayed eruption of teeth, absence of dentinogenesis imperfecta, normal hearing, and white sclera [11].

Type XIII

Fractures manifests after birth recurrently, hearing is normal and sclerae are white. They present a mild bone deformity, and

delayed tooth eruption, but they do not have dentinogenesis imperfecta. Radiographic examination of the skeletal system revealed bowing of the upper and lower limbs [11].

Type XIV

Characterized by huge degrees of severity with multiple fractures, that occurs prenatally or at approximately 6 years of age. Osteopenia, absence of dentitinogenesis imperfecta, normal sclera, and hearing have been reported [33].

Type XV

Phenotype variate from severity, ranging from mild to progressively deforming, which can occasionally lead to early infant death. They present short stature, no joint or skin hyperlaxity, sclera are white, and teeth appeared normal. Lumbar spine areal bone mineral density was very low [34].

Type XVI

Fractures can occur in uterus, at birth manifest short stature, multiple fractures, and soft calvarial bones and widely open fontanelles. During adolescence and also adults present blue sclerae, teeth are normal and progressive hearing loss [35].

Type XVII

No skeletal abnormalities were reported at birth. After birth manifest first fractures and may present multiple vertebral compression fractures of the thoracic spine and kyphoscoliosis. Sclerae are white and dentinogenesis are normal but they may have mild joint hyperlaxity [36].

Type XVIII

Prenatal fractures of ribs and long bones can occur. The present moderate short stature, blue sclerae, pectus carinatum, bowing of lower extremity long bones, variable scoliosis, chest deformity, striking tibial anterior angulation and generalized osteopenia [37].

Multiomics Analysis

Osteogenesis Imperfecta had been known since the early 1980s as a disease caused by mutations in either of the genes encoding type I collagen (COL1A1 and COL1A2). Since 2006, new mutations in collagen-related genes with different inheritance patterns have been found to cause OI [38]. During these 25 years' time lapse, diagnostic and research techniques have been improved. In 2001, the Human Genome Project (HGP) revealed for the first time the entire sequence of the human genome. This achievement has allowed a big work progress in biomedical research. Moreover, since 2007 the technical advancement of Next Generation Sequencing (NGS) has completely revolutionized the approach to DNA sequencing [39]. Through NGS, scientists can compare a large number of different genomes: this paved the way to many population studies. Furthermore, NGS makes it possible to compare the genome of a healthy individual with the genome of an affected individual and to find out gene(s) associated with a specific disease [40].

The NGS revolution applied to OI, combined with the traditional approaches, has unravelled since 2006 it's astonishing genetic heterogeneity: fifteen novel disease loci have been discovered in ten years' time [41]. Since 2006, seven of the disease genes discovered, cause AR forms of OI, encoding for proteins which are involved in collagen I modifications, processing, folding, cross-linking. Eight additional genes, whose defects cause either AR and AD forms, code for proteins involved in several osteoblast functions and survival. Moreover, epigenetic modifications of DNA (i.e., Cytosine methylation) it has been described as associated to de novo OI causing mutations [26], and contribute to explain recurrent *de novo* OI mutations. Scientific progress has prompted a few neologisms ending with -OMICS that refer to various study fields in biology, such as genomics, transcriptomics, proteomics, metabolomics. The related suffix -ome is used to address the study objects of such fields, such as the genome, transcriptome, proteome or metabolome, respectively. Genomics is an interdisciplinary research field focusing on the structure, function, evolution, mapping, and editing of genomes. A genome is a complete set of DNA, including all the genes of an individual. In contrast to genetics, which refers to the study of single genes and their roles in inheritance, genomics aims at the collective characterization and quantification of genes. Likewise, transcriptome refers to all RNA molecules in one cell or a cell population. Unlike DNA, which is the same in every somatic cell of an organism, RNA molecules reflect the expression profile of a specific cell type. Accordingly, proteomics and metabolomics represent the set of proteins and metabolites, respectively. Proteomics is used to quantify peptides abundance, modification, and interaction. Metabolomics simultaneously quantifies multiple small molecules, such as amino acids, fatty acids, carbohydrates, or other products of cellular metabolic functions. Metabolite levels and relative ratios reflect metabolic function, and out-of-normal range perturbations are often indicative of disease. Quantitative metabolite levels allowed the discovery of previously unknown genetic loci regulating small molecules, or their relative ratios, in plasma and other tissues [42,43]. Associated technologies include Mass Spectrometry (MS)-based approaches to quantify both relative and targeted small molecule abundances [44,45].

The omics field has been driven largely by technological advances that have made cost-efficient, high-throughput analysis of biologic molecules possible. Each type of omics data, on its own, typically provides a list of differences associated with the disease or with the population studied [46]. Novel and unexpected OI candidate genes have been identified since 2010 by means of -omics approaches, in table 3 an overview

about of OI-related genes identification from 1983 to 2016 [41]. Nevertheless, new OI disease genes are to be discovered, particularly in rare recessive forms which occur in inbred pedigrees not yet characterized at the molecular level. The candidate genes list is expected to grow in the near future, thanks to the combined -omics approaches.

Defective gene	Year	Methodological approach	OI type	Inheritance
COL1A1	1983	candidate gene	I,II,III,IV	AD
COL1A2	1984	candidate gene	I,II,III,IV	AD
IFITM5	2012	Wes, homozigosity mapping+targed NGS	V	AR
SERPINF1	2011	Wes, qwla+targed NGS	VI	AR
CTRP	2006	gwla in inbread families+candidate gene	VII	AR
P3H1 (LEPRE1)	2007	candidate gene	VIII	AR
PPIB	2009	candidate gene	IX	AR
SERPINH1	2010	candidate gene	X	AR
FKBP10	2010	homozigosity mapping+targed NGS	XI	AR
PLOD2	2012	homozigosity mapping+candidate gene	no type	AR
BMP1	2012	homozigosity mapping+candidate gene	XII	AR
SP7	2010	homozigosity mapping+candidate gene	XIII	AR
TMEM38B	2012	autozygosity mapping+wes	XIV	AR
WNT1	2013	wes+wgla+target ngs	XV	AR
CREB3L1	2013	candidate gene	XVI	AR
SPARC	2015	wes	XVII	AR
MBTPS2	2016	gwla+exome sequencing	XVIII	AR

Table 3: Years and method to identify the OI-related genes. Wes (Whole Exome Sequencing); gwla (Whole Genome Linkage Analysis); nsg (Next Generation Sequencing).

Diagnosis and Treatment

The fractures are the most important clinical features occurring in OI, even if 10% of OI patients have not reported fractures in long bone during childhood. Many patients develop the osteoporosis and levels of serum and urine markers of bone turnover (such as osteocalcin, alkaline phosphatase and amino-terminal telopeptide of type 1 collagen) associated to histomorphometry analyses help to perform OI diagnosis.

Often OI patients show blueness of the sclera, hearing loss, dentinogenesis imperfect, short stature, joint hypermobility [47]. In adult patients, cardiovascular complications may occur [48]. In particular, patients with OI type 1 is characterized by bone loss, blue-gray sclera and susceptibility to hearing loss in adolescence and young adult life while bone deformities is less frequent [47]. OI type 2 is extremely severe. Most fetus with OI type 2 are diagnosed prenatally and termination of pregnancy often occurs [47]. Patients with OI type 3 are diagnosed during the childhood and they show bone fragility and multiple fractures causing skeletal deformity. At the birth the sclerae may be blue and, generally, the sclerae become less blue with age [47]. Patients with OI type IV have osteoporosis and recurrent fractures with deformity of long bones [47]. Patients with OI type V are characterized by Calcification in Interosseous Membranes [49].

Unfortunately, there is no known therapy for the cure of osteogenesis imperfecta and the goal of treatment is addressed to prevent the skeletal deformities. As bone fragility is the most important feature of OI, the treatment aims to reduce osteoclastic activity. Therefore, bisphosphonates are considered the gold standard treatment for children with moderate to severe OI [50]. Immunotherapy, such as with Antisclerostin antibody, Cathepsin K antibody or anti-RANK-ligand antibody, has been proposed for improving bone mineral density in OI patients [51].

New therapeutic approaches are then required against OI. A challenge to counteract this genetic disease could be represented by the cell-based therapy based on the possibility of mesenchymal stem cells transplantation from health donors to OI patients. Preclinical studies have been conducted in OI murine models [52,53] and clinical attempts have been performed using whole bone marrow or fractionated MSCs in OI children [54,55] and a reduced number of fractures in these children have been reported by the authors [55]. However, further investigations need to be addressed to consider efficacy the cell-based therapy and new technologies such as CRISPR/Cas system, TALEN, and zinc-finger nucleases for genetic correction may be considered an important challenge to correct the DNA in adult cells.

Natural Evolution of OI

Musculoskeletal disorders and hearing issue are the most important organ compromised in adult OI. In a study

conducted in 37 patients, Sillence reported that foot pain, hearing deficit, and back pain are the most diffuse physical problems in OI patients [56]. The physical status of PI patients is usually evaluated on the basis of the ability to ambulate, the presence of fractures as well as the presence of deformities such as scoliosis or bowing [57,58].

The lungs are often compromised as the chest walls are greatly affected causing airway obstruction, hypertension in the pulmonary district and sleep apnea [59]. Scoliosis and pulmonary affections in OI patients are strongly correlated with reduced physical activity [60]. This finding is important as OI patients are sedentary and have an elevated BMI [61]. In severe OI respiratory diseases induce the death of the patients [61,62]. Dentinogenesis imperfect affects up to 50% of the OI patients [59]. Therefore, OI patients need frequent dental attentions.

Importantly, physical limitations influence the life quality of OI patients with consequences in the social field, self-image and independence. Interestingly, in a study conducted by administrating the questionnaires, the authors found that OI patients, although significant physical limitations, have high social achievement and employment. In addition, the authors reported that the inability to ambulate correlated with an elevate rate of unemployment [60].

Conclusion

Osteogenesis Imperfecta is a disorder arising from a large spectrum of genetic mutations. In the last years new genetic causes have been identified in OI disease even if most cases of OI are due to COLIA1/ A2 mutations. Therefore, further clinical investigations finalized to improve therapeutic approaches against the new genetic discoveries are needed.

Bone deformities and collagen defects induce important pathological conditions affecting various internal organs. There is not a known definitive cure for OI, and therapeutic treatment aim to prevent or reducing the symptoms. Cell transplantation as well as gene therapy could represent important challenges to counteract severe OI. However, these therapeutic approaches need further investigations.

Acknowledgments

We thank Dr. Cheri for helpful editing support in this work.

Conflicts of Interest

The authors declare no conflict of interest.

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