**Osteogenesis Imperfecta**

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**Basic Genetics and Disease Risks for other Family Members**

Over 90% of the cases of Osteogenesis imperfecta are caused by mutations in one of two genes, *COL1A1* and *COL1A2*. These genes code for protein chains of type I procollagen; proalpha1(I) and proalpha2(I). Type I procollagen is a trimer and an important protein in bone and other types of connective tissues. The mutant allele causes either a defect in the type I procollagen protein or reduces the amount of the protein produced.¹

There are multiple forms of Osteogenesis imperfecta and different mutant alleles are the cause. Type I results from mutations that produce premature stop codons in the *COL1A1* gene. These are often deletions or insertions of nucleotides in the exon regions of the gene that aren’t divisible by the number three. This often causes the mRNA produced to be unstable and reduces the amount of the type I procollagen produced.²

Osteogenesis imperfecta type II, III, and IV are often caused by substitutions for glycine in the triple helical domain of the proalpha chain.

Other forms of the disorder are caused by the production of proalpha chains with altered sequences. These mutations are often substitutions of glycine residues. As a consequence of this type of mutation, there is reduced procollagen formation and some protein is abnormal.¹

The different types of Osteogenesis imperfecta are inherited in different ways. Types I, II IV, and V are inherited as an autosomal dominant disorder. Type III is also inherited in an autosomal dominant form, but there are rare cases in which it can be inherited in a autosomal recessive manner. Type VII is inherited as autosomal recessive while the inheritance of type VI is still unknown.

The risk to family members is complicated by de novo mutations. The proportion of these cases varies with the severity of the disease. For example, almost 100% of individuals with severe forms of the disorder are new mutations while 60% of individuals with milder forms of the disorder are also de novo mutations. As a result, only 40% of patients with the milder form also have an affected parent.

If a parent is affected with an autosomal dominant form of the disease, then the siblings of a proband have a 50% chance of inheriting the disorder. In addition, offspring of an a proband have a 50% chance of being affected. The risk to other family members is dependent on the genetic status of the proband’s parents. If a parent is affected, his or her family members are at risk.

In a proband found to be carrying an autosomal recessive form of the disorder, the parents are obligate carriers of the mutant allele and would not be affected themselves. Siblings of the proband have a 25% chance of being affected, 25% chance of not being a carrier or being affected, and 50% chance of being carrier. As such, siblings found to be unaffected have a 2/3 chance of being a carrier. The offspring of a proband are obligate heterozygotes for the mutant allele. Each sibling of the proband's parents is at 50 % risk of being a carrier.
Biochemistry and Molecular Biology

Normal bone consists primarily of mineral derived from calcium and the protein collagen. In bone, collagen is derived from the protein products of two genes, proα1 \((COL1A1)\) and proα2 \((COL1A2)\). These gene products associate to form a trimeric protein consisting of two strands of proα1 and one strand of proα2; this association is initially electrostatic, but is later stabilized by the formation of disulfide bonds. Further modification of the chains forces the trimeric protein into a triple helical conformation. The procollagen is then exported from the cell, and in the extra cellular space terminal extensions are cleaved by specific N- and C-peptidases to form mature collagen. The newly formed mature triple helix then self aggregates to form fibrils. In bone, these fibrils serve as a matrix for the incorporation of hydroxyapatite crystals, the major mineral component of bone.³

Osteogenesis Imperfecta is a group of disorders that cause bone fragility and connective tissue abnormalities. Collagen is critical to both bone formation and is integral to connective tissue. Osteogenesis imperfecta shows a dominant inheritance pattern. Mutations in \(COL1A1\) that result in an allele from which no protein can be synthesized results in mild osteogenesis (type I). In this case only half the normal amount of collagen can be synthesized. This is a case of haploinsufficiency, 50% protein product is not sufficient for completely normal bone structure. However, mutations that result in a mutant proα1 protein that is synthesized, but not functional, cause much more severe cases of osteogenesis (types II, III, and IV). In this case, 50% of proα1 protein will be abnormal, but because bone collagen is a trimer of 2 strands of proα1 and one strand of proα2, 75% of completed collagen trimers will be abnormal. There is only one in four chance that two functional proα1 strands associate with one another to make functional protein. The abnormal collagen trimers are destroyed whole by cells. This includes the strands associated with the trimer that were normal. These forms of osteogenesis imperfecta are therefore examples of dominant negative disorders. When there is only one functional \(COL1A2\) gene, whether the gene is incapable of producing any protein, or produces a defective protein, the result is the same, there is only 50% of the normal amounts of collagen trimer. This is because only one strand of proα2 is incorporated into the trimer. Symptoms are relatively mild.³

Bone properties are determined primarily by two factors, collagen composition, and mineral content. Until recently, it was believed that mineral content was the primary factor responsible for bone strength. However, recent studies have uncovered an inverse correlation between bone fracture resistance and denatured collagen content. One study points to collagen composition as the primary indicator of bone fracture resistance, whereas mineral content corresponds to bone stiffness.⁴ This further supports the importance proα1 and proα2 in normal bone structure and explains phenotypic defects noted with \(COL1A1\) and \(COL1A2\) abnormalities. Collagen abnormalities also explain the blue discoloration of the sclera seen in some varieties of osteogenesis imperfecta, however the bone disorders are the far more troubling symptoms of osteogenesis imperfecta.

Recent advances have allowed for the development of mouse models of osteogenesis imperfecta that mimic both the phenotypes and biochemistry of osteogenesis imperfecta in humans. It is hoped that these models will allow for the further
investigation of the early development of skeletal tissue in osteogenesis imperfecta patients.5

Diagnostic Criteria, Prognosis for the Patient, and Treatments

As mentioned earlier, Osteogenesis imperfecta (OI) is classified as a group of disorders distinguished by fractures with little or no trauma and, later on life, hearing loss. The clinical features of OI represent a spectrum ranging from death to individuals with severe skeletal deformities, short stature, mobility problems, and to nearly asymptomatic individuals with a mild predisposition to fractures, normal lifespan and stature. Fractures can occur in any bone, but are most common in the extremities.1

The clinical diagnosis of Osteogenesis imperfecta at this juncture is based on family history, unique physical findings such as scleral hue, a history of fractures, imaging and radiographic findings. Radiographic findings include fractures of varying ages and stages of healing including osteopenia, “codfish” vertebrae, and wormian bones. Clinical features that help to differentiate OI from other conditions include age, characteristic triangular facies, blue sclerae, joint hypermobility, dental abnormalities, and, in adults, hearing loss.1

Analysis of bone biopsies is an accessory option to the diagnosis of OI type V and OI type VI. Biochemical testing which is an analysis of the amount and structure of type I collagen synthesized in vitro by cultured dermal fibroblasts detects abnormalities in 98% of individuals with OI type II, about 90% with OI type I, about 84% with OI type IV, and about 84% with OI type III. About 90% of individuals with OI types I, II, III, and IV (but none with OI types V, VI and VII) have an identifiable mutation in either COL1A1 or COL1A2. Most importantly, such testing is clinically available.1

In addition, if an abnormality associated with collagen has been identified in cultured cells from the proband, pre-natal testing of at-risk pregnancies can be performed by analysis of collagen synthesized by fetal cells obtained by chorionic villus sampling at about 10-12 weeks’ gestation. Testing in high-risk pregnancies can be performed by testing of COL1A1 and COL1A2 if the mutation has been identified in another affected relative. Prenatal ultrasound examination performed at a qualified institution in diagnosing OI, and done at the appropriate gestational age, can be effective in the prenatal diagnosis of the perinatal lethal form and most severe forms of OI prior to 20 weeks' gestation. However, it is important to note that fetuses affected with milder forms may be detected later in pregnancy when fractures or deformities occur.1

Management focuses on supportive therapy designed to maximize function while minimizing the effects of fractures and disabilities. In addition, clinicians should attempt to cultivate independence while maintaining the overall health of the patient affected with OI. Ideally, a multidisciplinary team is necessary including specialists in medical therapy of OI, orthopedics, and rehabilitation medicine. Considerable support is generally required by medical personnel to help parents feel comfortable caring for infants with OI type II.2 Promotion of appropriate physical activity, physical and occupational therapy for increased stability of bone, improved mobility, prevention of contractures, prevention of head and spinal deformity, endurance training, aerobic fitness, and muscle strengthening are good examples in how to treat OI patients. Also, fractures tend to be treated as they would in unaffected children and adults with special attention paid to shortening the immobility of children as much as remains practical. Casts should be light and small and
physical therapy should begin immediately following the cast removal. However, it is important to note that progressive spinal deformities are particularly difficult because of the poor quality of bone in severely affected children. Progressive scoliosis in severe OI does not respond to conservative management and response to surgical intervention may be limited.\(^6\)

References: