Osteogenesis Imperfecta

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About OI

- Osteogenesis imperfecta arises from an erroneous amino acid substitution during the formation of collagen
- This amino acid substitution is usually caused by a mutation in the COL1A1 or COL1A2 gene
- There are eight different types of OI
- OI is autosomal dominant, but may also arise from de novo mutations
- 6-7 affected people per 100,000
COL1A1 and COL1A2

- COL1A1 encodes type I collagen, a component in most connective tissues. It may be inactivated, or have amino acid substitutions in different types of OI. COL1A1 is located on the long arm of chromosome 17.

- COL1A2 is nearly identical in function to COL1A1, except that it is located on chromosome 7, and if mutated, tends to have symptoms of lesser severity.
Normal Collagen

• Collagen is the main protein component in connective tissues

• Collagen forms triple-helix fibrils, which constitute most of what we call fibrous tissue – i.e. tendons, ligaments, skin, bones, blood vessels, etc.

• Collagen also acts as part of the endomysium which blankets muscles
OI Collagen

• Substitution of cysteine for glycine in the collagen structure creates a bulge in the triple helix of the collagen fibrils

• The body thus hydrolyzes the mutated collagen, causing brittleness in the person’s bones
How each type works

- Type I: Collagen is of normal quality, but quantity is greatly diminished.
- Type II: Collagen is not of sufficient quality and quantity.
- Type III: Collagen is of normal quantity, but is improperly formed.
- Type IV: Collagen quantity is normal, but it is of a low quality.
- Type V: Same as type IV
- Type VI: Same as type IV
- Type VII: Caused by CTRAP gene mutation
- Type VIII: Caused by LEPRE1 gene mutation
Type I

• Caused by a mutation in the COL1A1 or COL1A2 gene
• Type I is most common form of Osteogenesis Imperfecta
Symptoms

• Blue Sclerae throughout life
• Hearing loss leading to tinnitus in about 50% of cases
• Multiple fractures arising from little injury
• Bruised skin, moderate joint hypermobility, hernias
• Mitral valve prolapse in roughly 18% (3X normal prevalence)
• Loose joints and poor muscle tone
Type II

- There are two types of OI type II, however both are characterized by perinatal fractures, severe bowing of long bones, and perinatal death from respiratory inefficiency.
- Collagen is of insufficient quantity and quality.
- Type IIA is autosomal dominant and is caused by a mutation in either COL1A1 or COL1A2.
- Type IIB is autosomal recessive, and is caused by a mutation in CRTAP gene.
CRTAP

• The CRTAP gene codes for the cartilage associated protein. This protein is required for post-translational hydroxylation of collagen.

• Mutations in this gene in OI type II cause the usual brittleness of the bones, and eventual respiratory failure, as well as a smaller head circumference, white or light blue sclerae, and ocular proptosis
Type III

• Heterozygous mutation in either COL1A1 or COL1A2

• This may be characterized as “Progressively Deforming” as though lifespan remains average, symptoms worsen with age

• Symptoms include usually normal sclerae, progressive deformity of limbs and spine – particularly during childhood and adolescence, short stature and vertebral curvature, bone brittleness, and sometimes dentiogenesis imperfecta
Type IV

• Caused by a mutation in either COL1A1 or COL1A2
• Collagen is of normal quantity, but substandard quality
• This type is characterized by normal sclerae, bone brittleness, short stature, and early loss of hearing
• Type IV may be further characterized as type IVA or type IVB depending on whether or not dentiogenesis imperfecta is present or not
Type V

• “Moderately deforming,” caused by COL1A1 or COL1A2 mutations, resulting in low quality collagen
• Fractures are frequent, but there is no dentiogenesis imperfecta, or blue sclerae
• There is a presence of hyperplastic calluses at fracture sites
• These calluses swell and harden over the site of injury, and may also arise spontaneously
Type VI

- This very rare type of OI is identical to Type IV with a few differences
- Affected people have more fractures in their lives, and also have increased serum alkaline phosphatase levels, something that contributes to decreased levels of mineralization in bones
- Type VI is most likely recessive, though the method of inheritance isn’t fully understood
Type VII

• Type VII is unique in that it is caused by a mutation in the CRTAP gene regulating cartilage associated protein, and is inherited recessively.

• If CRTAP is nonfunctioning, the result is universally lethal.

• Normally, CRTAP function is near 10% in Type VII OI patients, leading to short stature, hip deformities (coxa vara), and bone fragility.
Type VIII

- Caused by a recessive mutation in the LEPRE1 gene
- This gene is important in the body’s process of collagen, and works along with CRTAP. LEPRE1 modifies proline in collagen molecules, a step critical to collagen assembly and folding.
- OI type VIII is characterized by highly brittle bones, short stature, and extreme under-mineralization of bones.
Treatments

• There presently is no cure for OI
• Drugs such as Fosamax and Pamidronate may be used to treat bone brittleness, but are not fully FDA approved
• Physiotherapy and physical aids may assist OI patients
• Metal rods may be implanted surgically to improve strength in the long bones