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

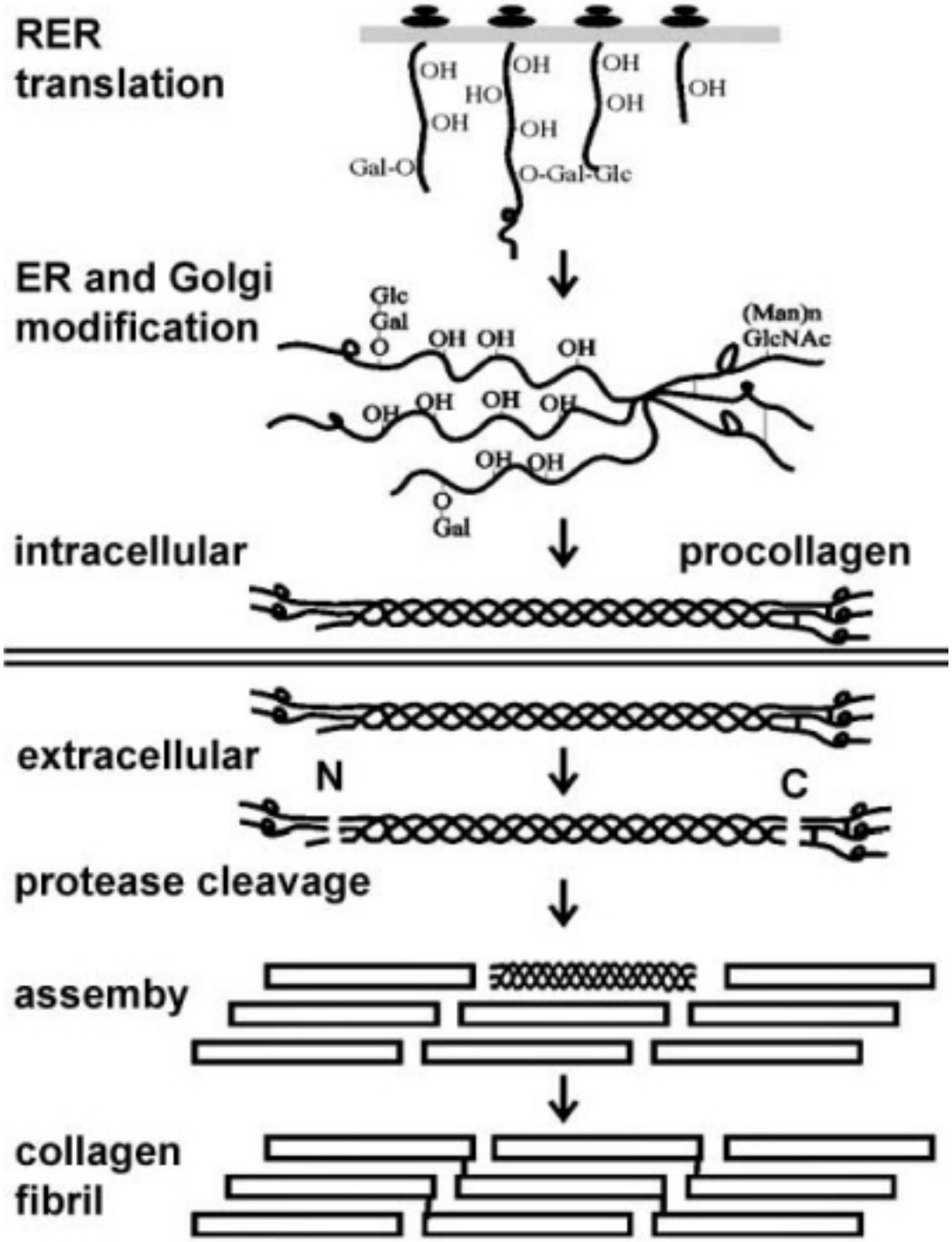
- COL1A1 encodes type I collagen, a component in most connective tissues. It may be inactivated, or have amino acid substitutions in different types of OI. COL1A1 is located on the long arm of chromosome 17.
- COL1A2 is nearly identical in function to COL1A1, except that is is located on chromosome 7, 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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How each type works

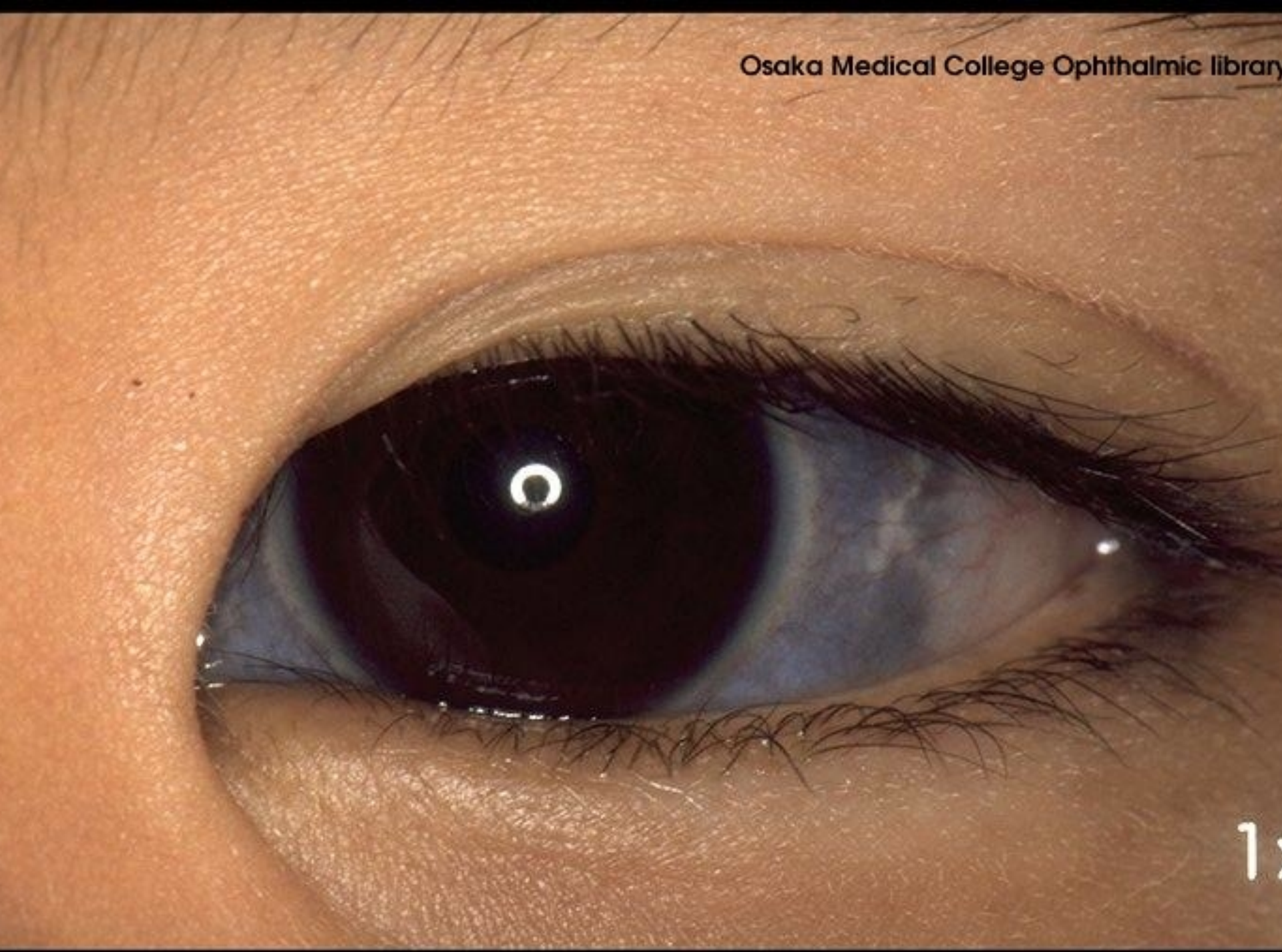
- Type I: Collagen is of normal quality, but quantity is greatly diminished.
- Type II: Collagen is not of sufficient quality and quantity.
- Type III: Collagen is of normal quantity, but is improperly formed.
- Type IV: Collagen quantity is normal, but it is of a low quality.
- Type V: Same as type 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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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

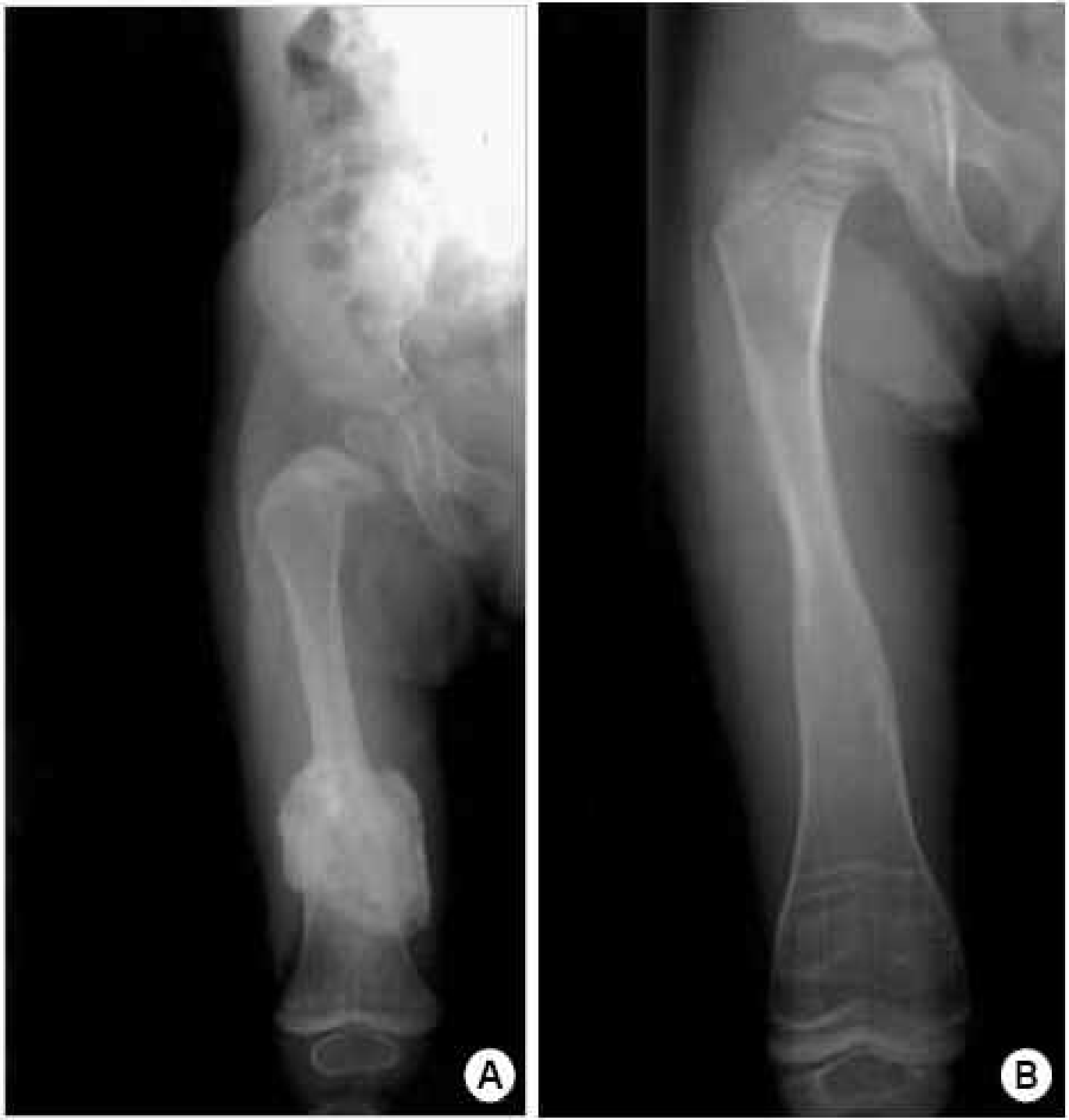
- Heterozygous mutation in either COL1A1 or COL1A2
- This may be characterized as “Progressively Deforming” as though lifespan remains average, symptoms worsen with age
- Symptoms include usually normal sclerae, progressive deformity of limbs and spine – particularly during childhood and adolescence, 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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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
- Physiotheraphy and physical aids may assist OI patients
- Metal rods may be implanted surgically to improve strength in the long bones