COL1A1-2-Related Osteogenesis Imperfecta

Genetics

-Gene: COL1A1 (Collagen α1(I) chain; 17q21.33), COL1A2 (Collagen α2(I) chain; 7q21.3)

-Encode the two chains pro α1(I) and pro α2(I) of type I procollagen --> collagen type I is a heterotrimer consisting of two α 1 chains and one α 2 chain

-AD and rare AR; penetrance 100%

-De novo: 60% of type I and type IV; close to 100% of type III; 100% of type II

Clinical findings/Dysmorphic features

-Fractures with minimal trauma; dentinogenesis imperfecta (DI); blue sclera; adult-onset HL

-Continuum: perinatal lethality - severe skeletal deformities/mobility impairments/very short stature - nearly asymptomatic ind. with mild predisposition to fractures/normal dentition/normal stature/normal life span

-Fractures can occur in any bone, but are most common in extremities

-DI: gray or brown teeth, may appear translucent, wear down and break easily

-Four types of COL1A1/2-related OI:

-OI type I: classic non-deforming OI with blue sclerae

-OI type II: perinatally lethal OI

-OI type III: progressively deforming OI

-OI type IV: common variable OI with normal sclerae

Etiology

-Prevalence of approximately 6-7:100,000

Pathogenesis

-Type I (diminished collagen production): most ind. with type I have premature STOP codon in one COL1A1 allele --> half the normal quantity of type I procollagen molecules; some with SNVs --> amino acid change is located in amino terminus (amino terminal changes tend to be less disruptive --> collagen chain assembly can still initiate as usual at the carboxy terminus)

-Types II, III, and IV (structurally defective collagens): mutations produce structurally abnormal proα1(I) or proα2(I) chains; mostly substitutions in triple helix that replace a glycine with a more bulky residue --> disrupts formation of triple helix; ratio wt to mut collagen is 1:3 if proα1(I) is mutated and 1:1 if proα2(I) is mutated

-Phenotype depends on: specific collagen affected, location of the substitution, nature of the substituting residue, but:

--> Substitutions in proα1(I) more in patients with OI types III and IV and more often lethal

--> Replacement of glycine (neutral) with charged (aspartic acid, glutamic acid, arginine) or large residue (tryptophan) --> very disruptive and associated with severe (type II)

Genetic testing/diagnosis

-Diagnosis:

1) Family history, a history of fractures, characteristic physical findings

2) X-ray: fx of varying ages/stages of healing, wormian/intrasutural bones, "codfish" vertebrae, osteopenia)

3) Molecular testing of COL1A1 and COL1A2 and/or biochemical analysis of type 1 collagen

-Biochemical testing (i.e. analysis of structure and quantity of type I collagen synthesized in vitro by cultured dermal fibroblasts)

-Suggested diagnostic work flow:

1) Sequencing of COL1A1/2 (eventually follow-up studies to determine pathogenicity)

2) Deletion/duplication analysis (detects additional 1%-2% of pathogenic variants)

3) If no causative COL1A1/2 variant is found, re-review clinical data --> proceed to screening for the non-COL1A1/2-related genetic disorders

Others

-Treatment: bisphosphonates (slow down bone resorption by shortening the life of osteoclasts and prolonging the life of the osteoblasts)