Osteogenesis Imperfecta

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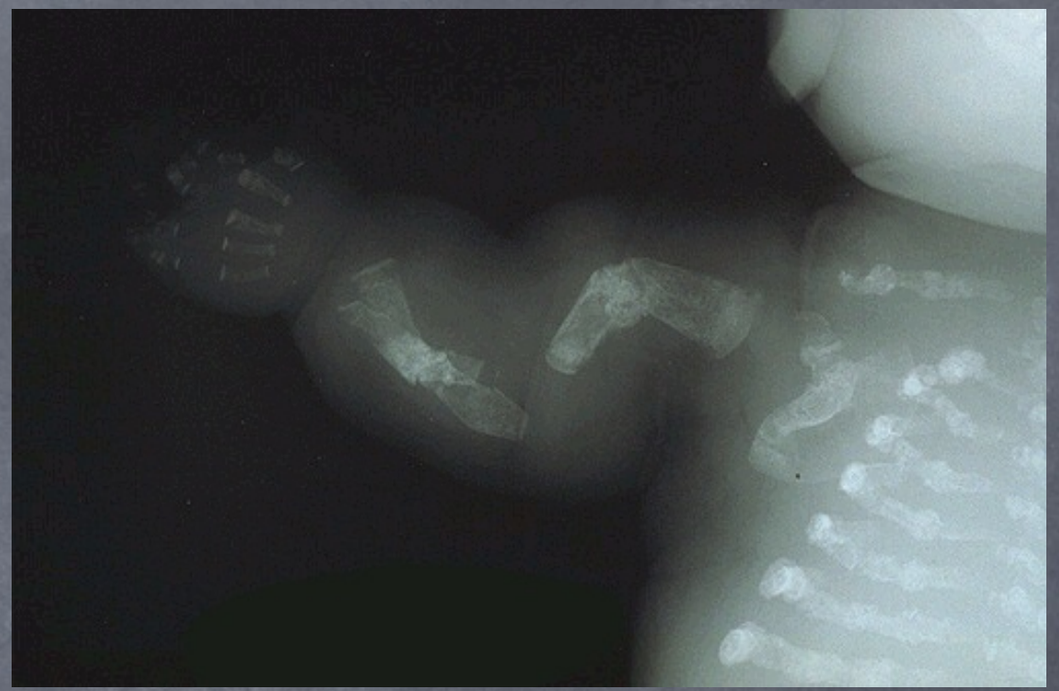
The Brittle Bone Disease



"Imperfect Bone Formation"

Congenital

Caused by various gene mutations that affect Collagen
-Type 1 Collagen Critical Bone Structure
-Severity of defect impacts severity of OI

8 Different types- various characteristics/mutations/consequences

Affects 6-7/100,000 People World Wide (I and IV most common)

4 Genes

COL1A1,COL1A2, CTRAP, AND LEPRE1

COL1A1/COL1A2
-Cause more than 90% of OI cases
-Types I,II,III,and IV
-Similar function- produce Type I collagen
-Different Chromosome Locations/Severity
-Type I- Premature termination of codons
-Type II,III,IV-Amino Acid Substitution of Glycine
-Functional Consequence: Deficiency of Collagen/Fail to Produce Enough

CTRAP/LEPRE1
-Rare, severe cases (although II is the most severe type)
-Functional Consequence: Disrupt production of Collagen Molecules themselves
-CTRAP-TypeVI /LEPRE1-Type VIII

*NOT all genes known- still cases found without an identified mutation in any of the 4 genes

Inheritance

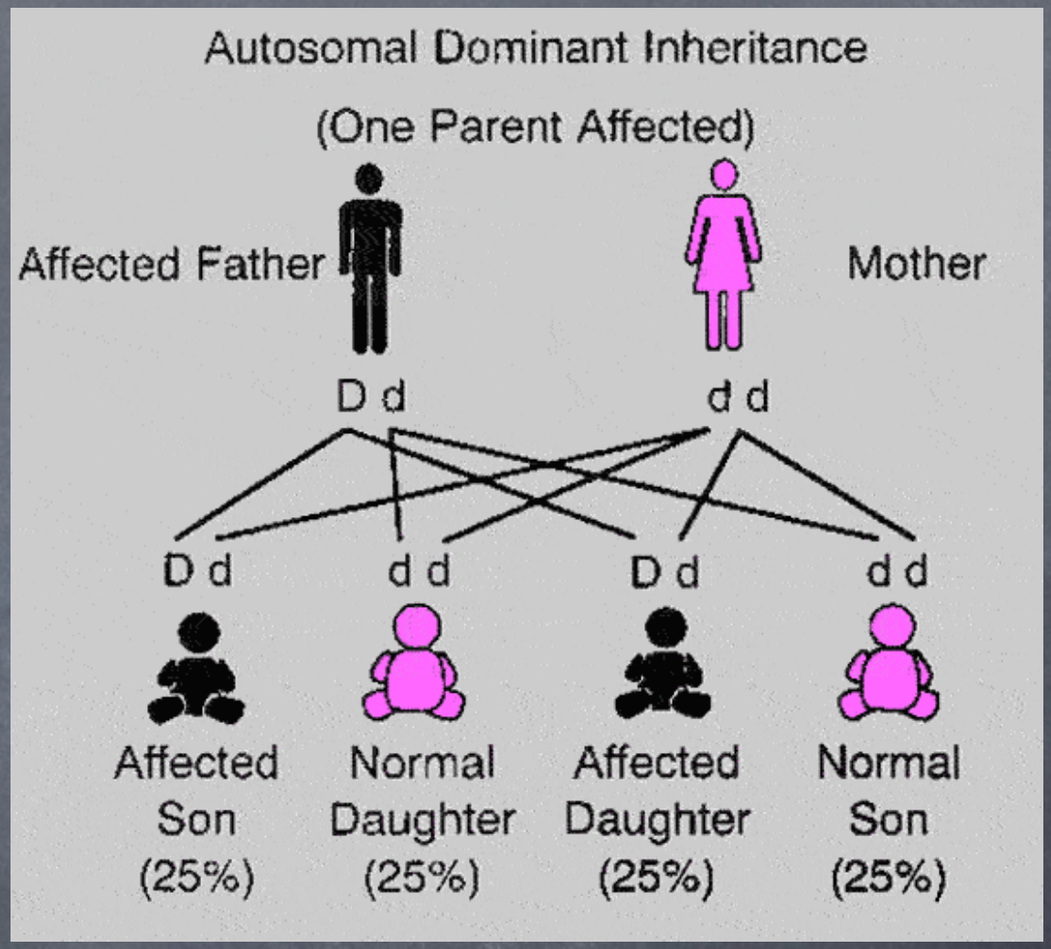
Variance

Most common: Autosomal Dominant

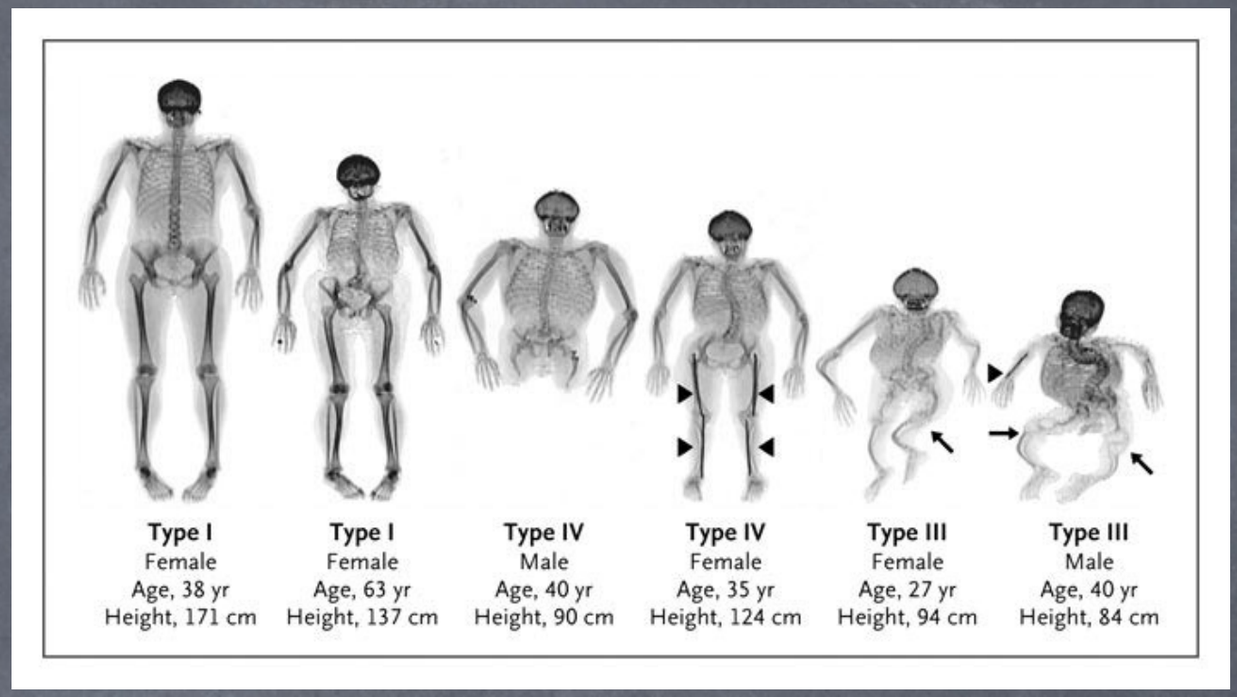
Some cases (type VII) found to be Autosmal Recessive

35% Cases found to be De Nova Mutation

Full Penetrance for Autosmal Dominant



Types of OI



Key Distinguishing Factors-
Collagen Quality and Quantity based on mutation

Genetic Differences/Mutations used to Classify Types

(COL1A1/COL1A2)
I-Sufficient Quality/Insufficient Quantity (*Most Common)
II-Insufficient Quality/Insufficient Quality
III-Insufficient Quality (poor formation)/Sufficient Quantity
IV-Insufficient Quality/Sufficient Quantity
V/VI-Very similar to IV with different histologic features

Thus: Type I most mild OI//Type II most severe OI
Rest of Types fall between

VII/VIII
-Very rare
-Autosomal Recessive

Prognosis

Depends on type of OI:

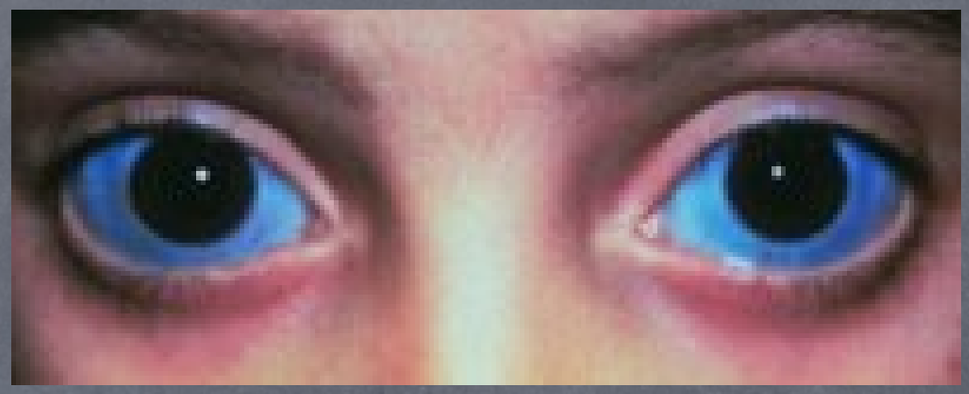
Type I – normal lifespan.

Type II – death in the first year of life.

Type III–wheelchair bound and usually have a shortened life expectancy.

Type IV– often need braces or crutches to walk. Life expectancy normal or near normal.

Characteristic Symptoms



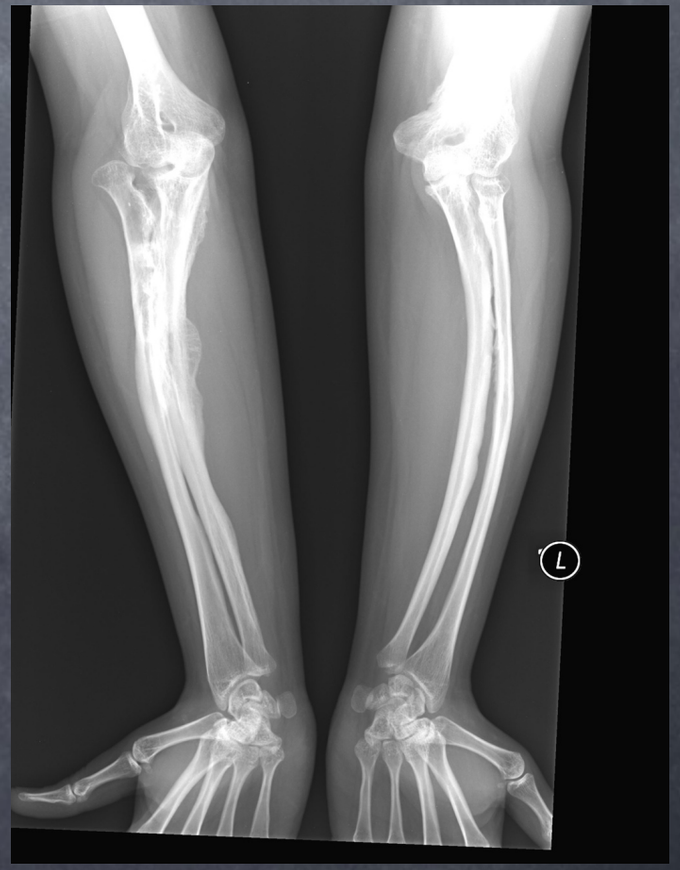
Symptoms Vary According to OI Type:

-Bone fractures in childhood/adolescence from Mild trauma
-Fractures before birth or little/no trauma
-Blue Sclerae
-Kyphoscoliosis
-Short Stature
-Respiratory Problems
-Ribcage fragile/deformed-infants have trouble breathing and die almost immediately
-Hearing loss
-Dentinogenesis Imperfecta

Diagnostics

Classical:
X Rays can reveal fractures and bone deformities to confirm symptoms

Novel:
Collagen analysis from skin biopsy to check for types/quantities collagen present
Gene/DNA analysis to examine characteristic mutant genes
DNA sequencing can now find close to 100% of mutations in COL1A1 and COL1A2 genes



Treatments

Currently No Cure

Classical:
Essentially Treatment of Manifestations/Symptoms
Therapy,Physical Medicine, Orthopedic, Surveillance (children), Dental

Novel:
Gene Therapy difficult because of many gene variations
Bisphosphonates to prevent loss of bone mass (under evaluation)
Injection of Human Growth Hormone (under evaluation)
Bone Marrow Transplant (under evaluation)

History

Recognized in Egyptian Mummy from 1000 BC

Most Notable Case- Ivan the Boneless, Prince of 9th Century Denmark

Carried on shield to battle because unable to walk on “soft legs”

Nabil Shaban, actor- documentary: The Strangest Viking

1918 Dr. Van der Hoeve described fragile bones, blue sclera,and deafness as distinct inherited syndrome

1970’s Dr. David Sillence developed “Types” Categorization combining clinical symptoms with genetic component