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Clinical info

15 week ♀ foetus
   - Ultrasound: dysplasia of long bones
     - couple’s third affected foetus

   - No other malformation
Family history

Maternal grandmother affected

Mother (II-2) affected:
- 50th %ile at birth
- 10th centile at 6 y.o.a.
- 5th centile at 10 y.o.a.
- **< 5th** centile in adulthood
- Face, trunk, skin, hair, nails & teeth N
- Disproportionately short limbs
- Femoral fracture at 9 y.o.a.
- Health otherwise normal
Macroscopic exam

15 week ♀ foetus

Dilatation & Curettage
- varus deformity of both feet
from Potter 2007

Normal growth plate - fetal bone

Resting  Prolif  Hypertrophy  Coalescence  Column
Abnormal column formation
Deficient ossification
Hypocellular resting cartilage
Abnormal column formation
Cytoplasmic inclusions

PAS-D, 400x
Cytoplasmic inclusions

MED:
similar inclusions found in matrilin-3 and COL-IX mutations

PAS-D, 630x
Diagnosis: Pseudoachondroplasia

COMP gene: G → A substitution
- amino acid D437N substitution
  - aspartic acid (negatively charged aa) is replaced by asparagine (a neutral aa)
Pseudoachondroplasia

MIM abbreviation: PSACH
(alternative MIM: spondyloepiphyseal dysplasia)

MIM # 177170

#: gene responsible is known – Cartilage Oligomeric Matrix Protein (COMP)
COMP & MED type 1

A mutation of the same gene (COMP) can present as Multiple Epiphyseal Dysplasia type 1 (MED-1)

Similar but milder phenotype than PSACH (MIM # 132400), with similar PAS-D inclusions in rER
COMP functions

COMP present in ECM of cartilage, tendons and ligaments

binds 14 Ca++ (required for protein folding in the rER)

binds Col-I, -II, -III & -IX (Zn-mediated)
- mutations decrease binding
COMP: from gene to ECM

- COMP-gene (splicing) → COMP-mRNA
- COMP-protein (post-ribosome & Golgi modifications)
- Transmembranous secretion
- COMP-proteins bind Col-1, -2, -3, -9 & -11

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Normal COMP

COMP, Col-9 & matrilins provide the interface between fibrillar matrix (Col-II & -XI) & extra-fibrillar matrix (aggrecan, a proteoglycan)

COMP promote cell attachment through binding integrins on cell membrane,
and molecules of the ECM (collagens, fibronectins, etc.)
COMP pathology

Mutant COMP: intracellular accumulation & dose-dependant chondrocyte cytotoxicity

Growth failure 2\textsuperscript{ry} to chondrocyte death in growth plate

Accumulation in ER (ER-storage disease, 2\textsuperscript{ry} to abnormal folding and processing of COMP protein)
In the rER, mutated COMP binds with collagen, chondroitin sulfate proteoglycan 1 and link protein to form large insoluble cytotoxic « inclusion bodies »
COMP pathology

ECM collagen fibers disorganized
- dominant interference of mutated COMP with collagen fiber assembly in cartilage and tendons

Comp^-/- mice have a N. phenotype → disease is caused by abnormal protein (cytopathic effect & role in collagen assembly)
Multiple Epiphyseal Dysplasia-1

Genetically heterogeneous syndrome:

MED-1 can be caused by abnormal COMP

MED-1 can also be caused by:
- abnormal COL-IX (COL9A1, COL9A2 & COL9A3)
- abnormal MATRILIN-3 (MATN3)
- abnormal solute carrier member 26, member 2 (SLC26A2)
Cohen 2006
The new bone biology
Am J Med Genet (part A)
COMP: Functions

Normal interaction with Col-9 & Col-2

Normal interaction with matrilin-3

Binding to growth factors regulating chondrocyte proliferation
COMP: Dominant negative mutation

Normal COMP-protein

Abnormal COMP-protein

Normal interaction with Col-9 & Col-2

Abnormal interaction with Col-9 & Col-2 disrupts normal Col-2 & Col-11 scaffolding

Normal interaction with matrilin-3

Abnormal structure of COMP prevents binding with matrilin

Binding to growth factors regulating chondrocyte proliferation

Loss of binding site disrupts chondrocyte proliferation

Cytotoxic accumulation in ER
Normal COMP-protein

Abnormal COMP-protein

Abnormal configuration

Abnormal Ca++ binding site

Abnormal glycosylation

Abnormal EGF-like domain

Normal interaction with collagen and other proteins of the extra-cellular matrix

Genotype / Phenotype
Genotype / Phenotype (Allelic variants) > 100 COMP mutations reported

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CHU Sainte-Justine
References

OMIM (On-line Mendelian Inheritance in Man)

http://omim.org/entry/177170?search=psach&highlight=psach

http://omim.org/entry/600310?search=psach&highlight=psach
References


References

