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Audiologic and Genetic Determination of Hearing Loss in Osteogenesis Imperfecta

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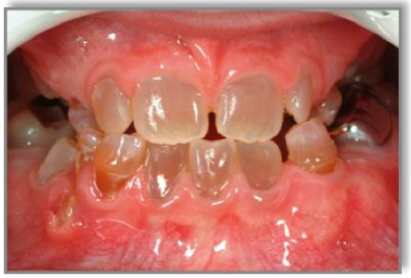
Osteogenesis imperfecta (OI)

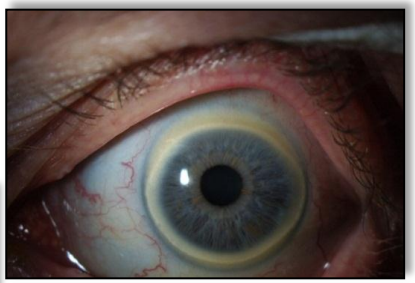
Prevalence

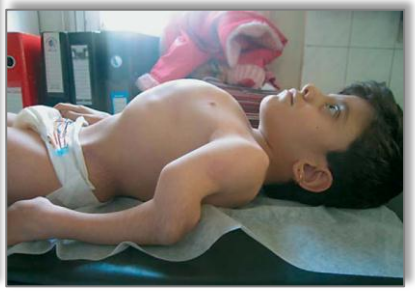
- 1/10.000

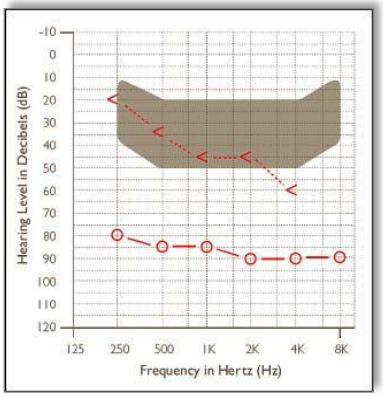
Phenotype

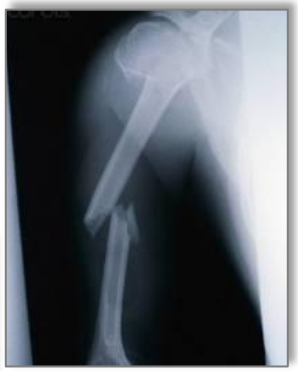
- Bone fragility
- Scoliosis
- Bone deformities
- Short stature
- Blue sclerae
- Dental abnormalities
- Hearing loss (50%)

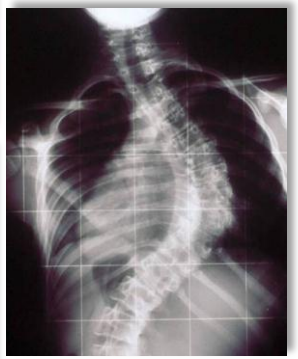


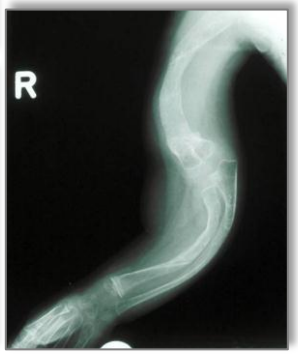












Osteogenesis imperfecta (OI)

Classification

Type	Severity	Inheritance	Mutated gene
I	Mild	AD	*COL1A1/COL1A2*
II	Lethal	AD	*COL1A1/COL1A2*
III	Severe	AD	*COL1A1/COL1A2*
IV	Moderate	AD	*COL1A1/COL1A2*
V	Moderate	AD	Unknown
VI	Moderate-severe	AR	*SERPINF1*
VII	Severe/lethal	AR	*CRTAP*
VIII	Severe/lethal	AR	*LEPRE1*
IX	Moderate to lethal	AR	*PPIB*
X	Severe to lethal	AR	*SERPINH1*
XI	Severe	AR	*FKBP10*

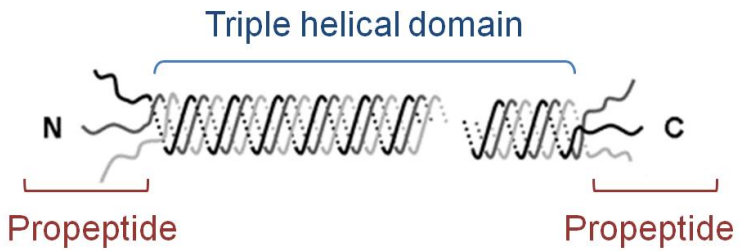
90 %

5%

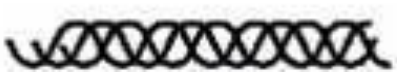
AD: autosomal dominant; AR: autosomal recessive

Genotype

- 90%: autosomal dominant mutation in
  COL1A1
  COL1A2
  → Type I collagen



- ≥ 1000 distinct mutations
- Type I collagen synthesis:

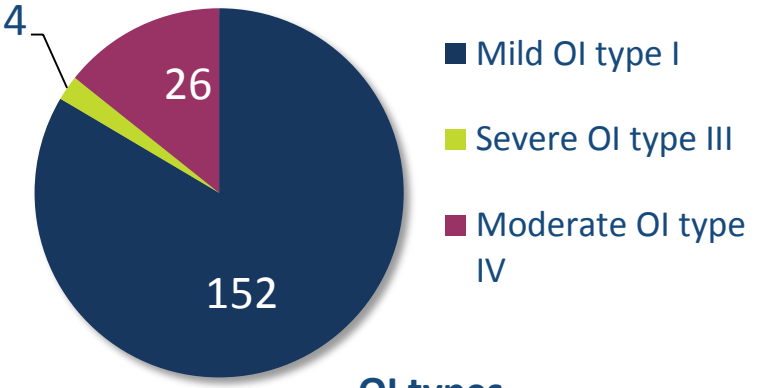
Normal	OI Quantitative defect	OI Qualitative defect
		
	Mild type I	• Mild type I • Lethal Type II • Severe type III • Moderate type IV

Research aims

- Audiologic characterization
- Radiologic evaluation
- Correlating the audiologic phenotype to the genotype

Subjects:

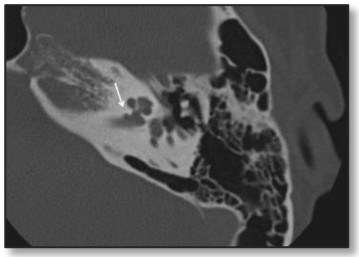
- N=182 (84 Belgian, 67 Dutch, 31 Italian)
- Mean age: 30.2 y. (SD:16,9; 3-89 y)



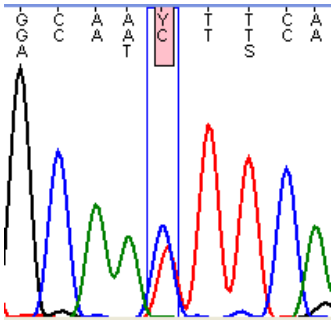
OI types

Measurements/analyses:

Audiometry



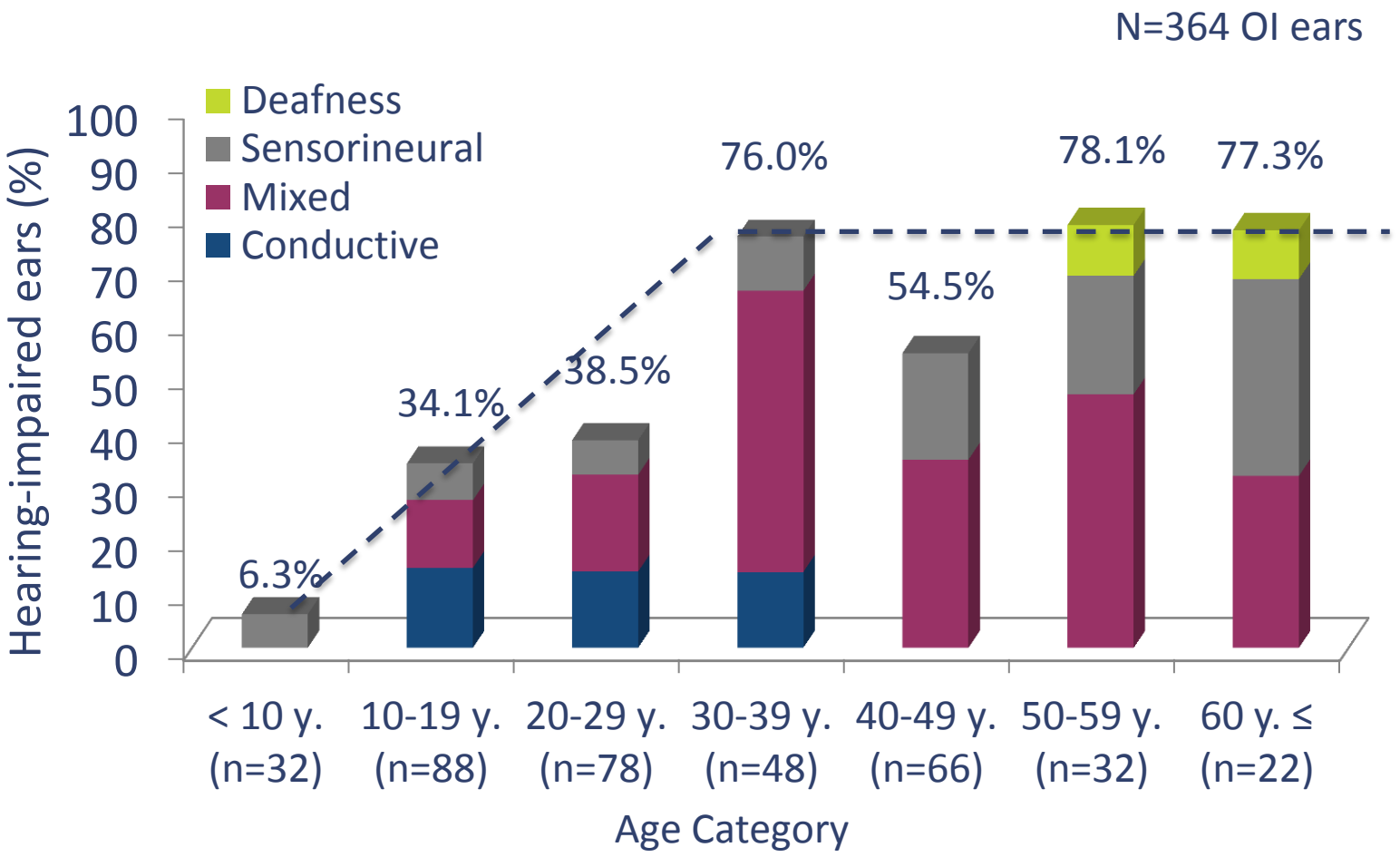
Temporal bone imaging



Genotype assessment

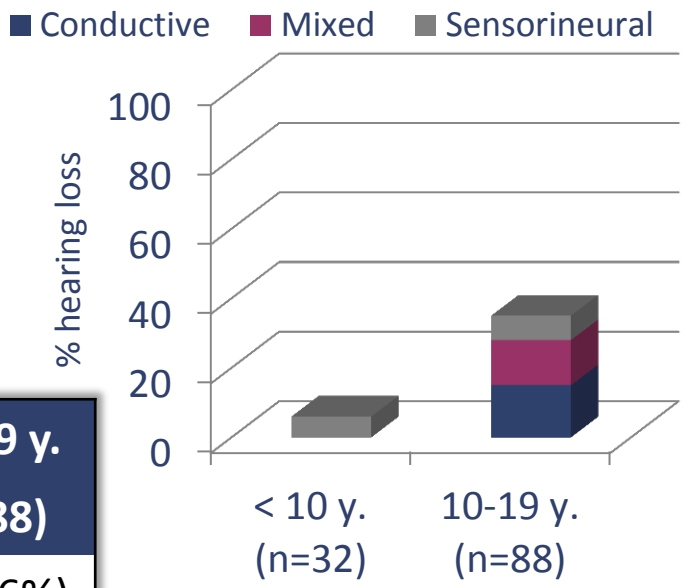
Introduction
Methods
Results
Conclusion

1. Audiologic phenotype (1)



1. Audiologic phenotype (2)

Pediatric population

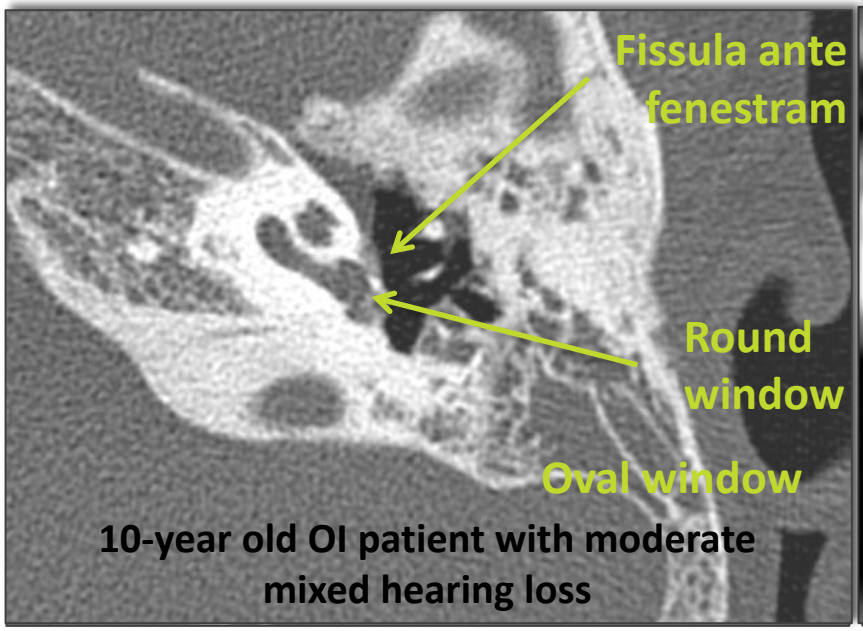


Audiologic phenotype	0-9 y. (n=32)	10-19 y. (n=88)
Normal	30 (94%)	58 (66%)
Hearing loss	2 (6%)	30 (33%)

2. Radiologic characterization

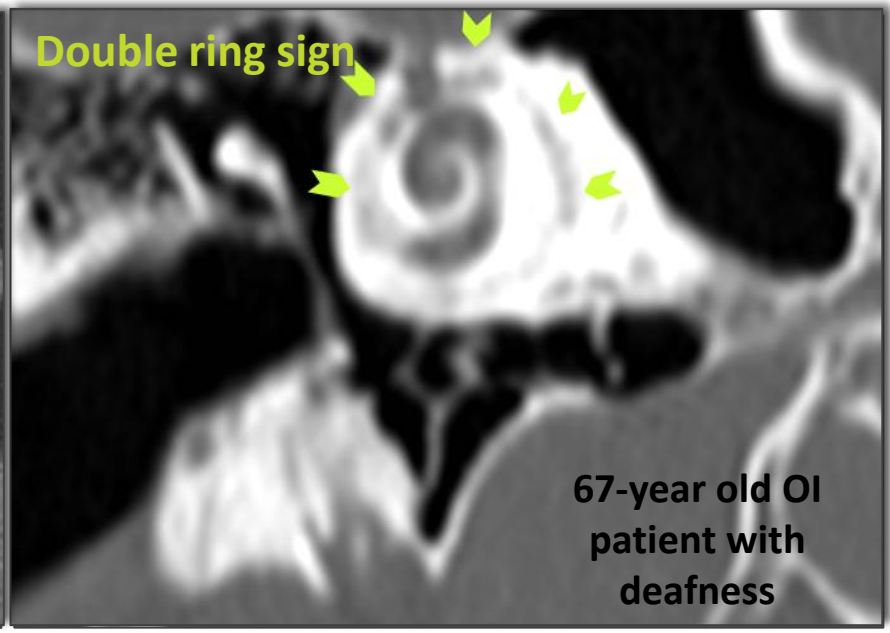
- Computed tomography (CT) images of temporal bone
- 17 hearing-impaired OI patients (conductive or mixed)

Fenestral hypodensities



~ air-bone gap

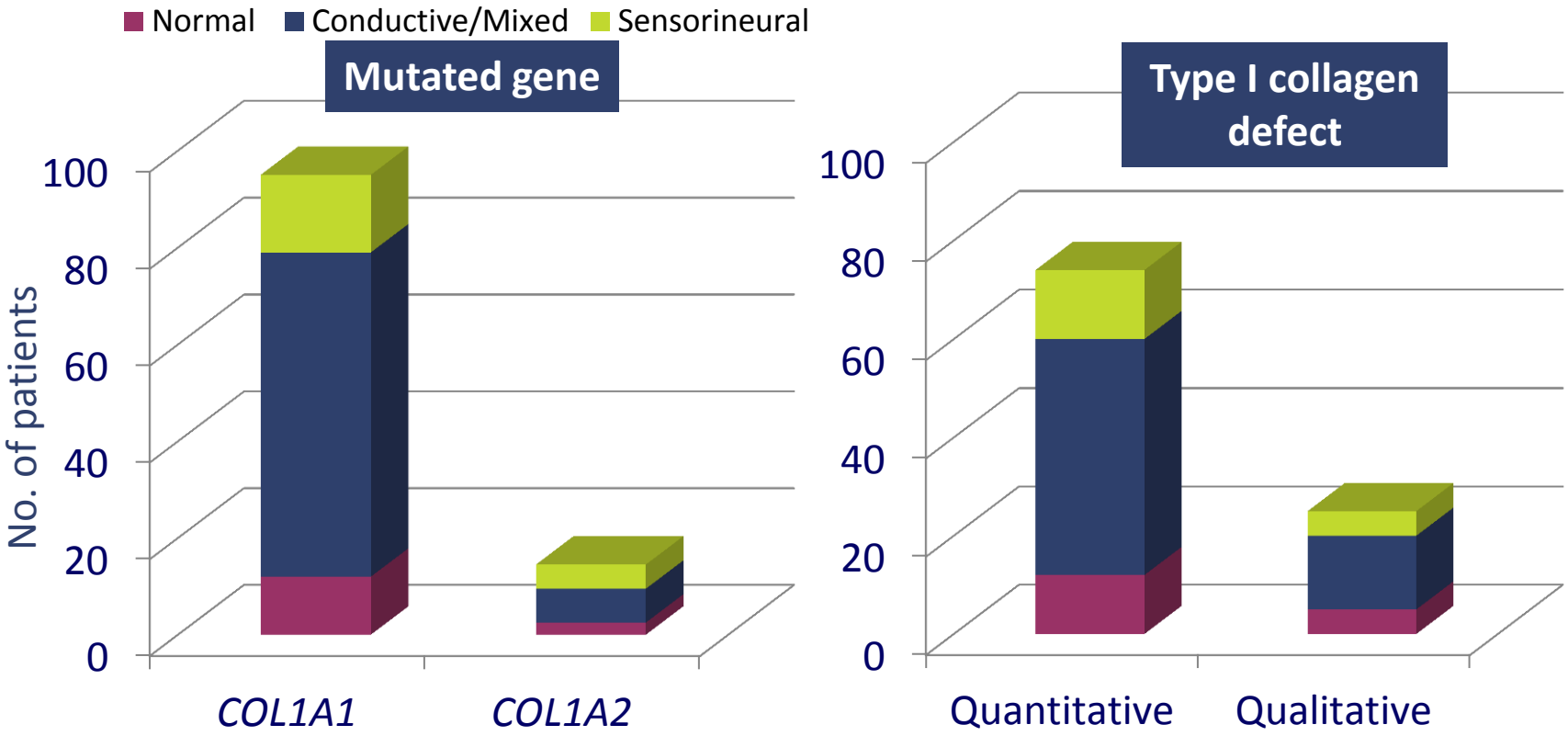
Retrofenestral hypodensities



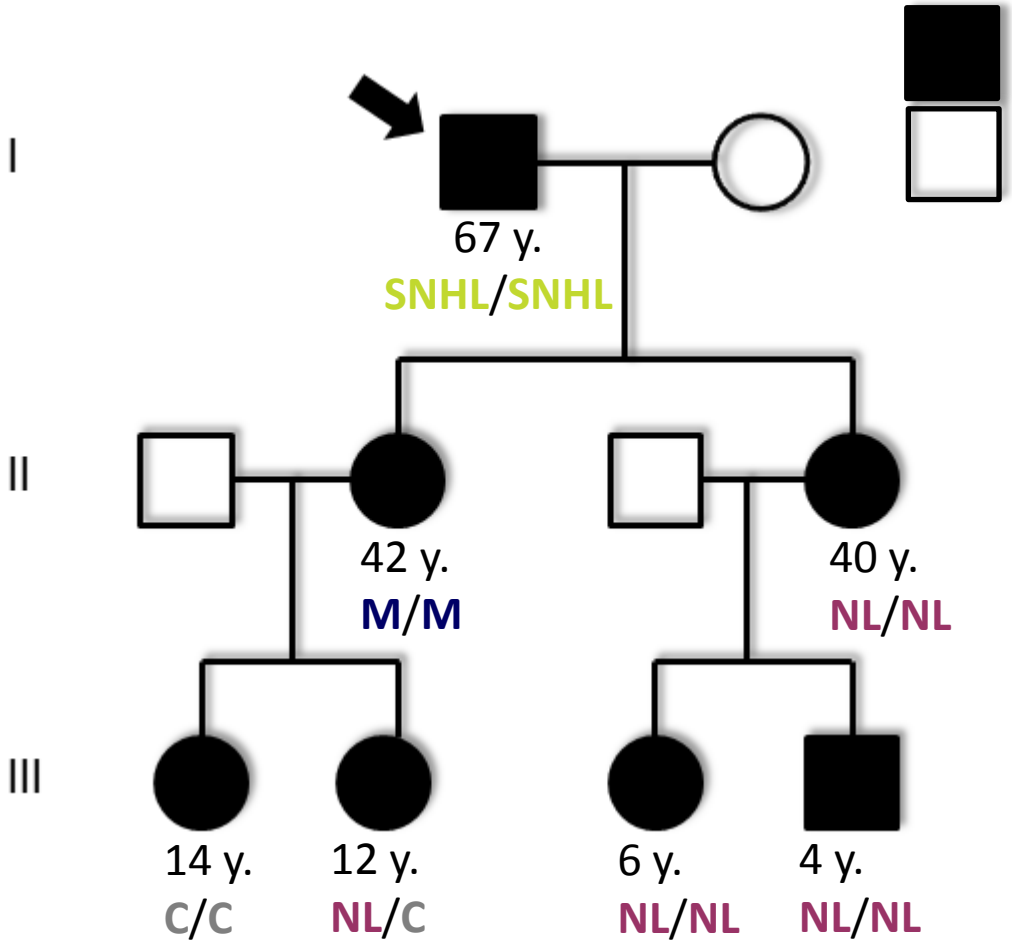
~ bone conduction threshold

4. Audiologic phenotype-genotype correlation in OI (1)

- 114 OI subjects
  - Hearing-impaired (conductive/mixed/sensorineural)
  - Normal hearing and age ≥ 40 y.



4. Audiologic phenotype-genotype correlation in OI (2)



SNHL sensorineural
M mixed
C conductive
NL normal hearing

Intrafamilial variability in audiologic phenotype

5. Genetic modifiers for hearing loss in OI

- No correlation between audiologic phenotype and *COL1A1*/*COL1A2* mutation
- Additional genetic trigger?

- Clinical similarities with otosclerosis

→ Associated with SNP T263I in *TGFB1* (protective)*

Audiologic phenotype	C allele n (%)	T allele n (%)
Normal hearing	18 (17.3)	0 (0.0)
Hearing loss	86 (82.7)	5 (100.0)
○ *Conductive/mixed hearing loss*	*70 (67.3)*	*3 (60.0)*
○ *Pure sensorineural hearing loss*	*16 (15.4)*	*2 (40.0)*

→ **Audiologic phenotype in OI is NOT associated with SNP T263I in *TGFB1***

*Thys et al. (2007) The coding polymorphism T263I in TGF-beta1 is associated with otosclerosis in two independent populations. *Hum Mol Genet*;16(17):2021-2030.

Conclusion

Audiologic phenotype in OI

- Heterogeneous, intrafamilial variability
- Hearing loss may develop in childhood, usually before 40y.
- Regular follow-up recommended
- No association with *COL1A1/COL1A2* mutation
- No association with SNP T263I in *TGFB1*

Future perspectives

- Genetic modifiers for hearing loss
- Effect of pharmacological treatment (bisphosphonates) on hearing

Thank you

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