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

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

AD: autosomal dominant; AR: autosomal recessive
**Genotype**

- 90%: autosomal dominant mutation in *COL1A1* and *COL1A2* → Type I collagen
- ≥ 1000 distinct mutations
- Type I collagen synthesis:

<table>
<thead>
<tr>
<th>Normal</th>
<th>OI Quantitative defect</th>
<th>OI Qualitative defect</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Normal collagen structure" /></td>
<td><img src="image2" alt="Quantitative defect" /></td>
<td><img src="image3" alt="Qualitative defect" /></td>
</tr>
</tbody>
</table>

- 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)

Measurements/analyses:
- Audiometry
- Temporal bone imaging
- Genotype assessment

OI types:
- Mild OI type I
- Severe OI type III
- Moderate OI type IV
1. Audiologic phenotype (1)

N=364 OI ears

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Deafness</th>
<th>Sensorineural</th>
<th>Mixed</th>
<th>Conductive</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 y.</td>
<td>6.3%</td>
<td>34.1%</td>
<td>38.5%</td>
<td>22.1%</td>
</tr>
<tr>
<td>10-19 y.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29 y.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 y.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49 y.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 y.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 y. ≤</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hearing-impaired ears (%)
## 1. Audiologic phenotype (2)

### Pediatric population

<table>
<thead>
<tr>
<th>Audiologic phenotype</th>
<th>0-9 y. (n=32)</th>
<th>10-19 y. (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30 (94%)</td>
<td>58 (66%)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2 (6%)</td>
<td>30 (33%)</td>
</tr>
</tbody>
</table>

![Bar chart showing audiologic phenotype by age group](chart.png)

- Conductive
- Mixed
- Sensorineural

### Results

- Normal hearing: 94% (0-9 y.) vs. 66% (10-19 y.)
- Hearing loss:
  - Mild (20-40 dB HL): 6% (0-9 y.) vs. 12% (10-19 y.)
  - Moderate (40-70 dB HL): 20% (10-19 y.)
  - Severe (70-95 dB HL): 1% (10-19 y.)
2. Radiologic characterization

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

Fenestral hypodensities

- Fissula ante fenestram
- Round window
- Oval window

10-year old OI patient with moderate mixed hearing loss

~ air-bone gap

Retrofenestral hypodensities

- Double ring sign

67-year old OI patient with deafness

~ 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.

![Graph showing the correlation between mutated gene types and hearing impairments.](image)

- COL1A1
  - Normal: 50
  - Conductive/Mixed: 50
  - Sensorineural: 10

- COL1A2
  - Normal: 20
  - Conductive/Mixed: 20
  - Sensorineural: 0

![Graph showing type I collagen defect.](image)
4. Audiologic phenotype-genotype correlation in OI (2)

Intrafamilial variability in audiologic phenotype

<table>
<thead>
<tr>
<th>Age</th>
<th>Genotype</th>
<th>Hearing Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 y.</td>
<td>SNHL/SNHL</td>
<td></td>
</tr>
<tr>
<td>42 y.</td>
<td>M/M</td>
<td>M (mixed)</td>
</tr>
<tr>
<td>40 y.</td>
<td>NL/NL</td>
<td></td>
</tr>
<tr>
<td>14 y.</td>
<td>C/C</td>
<td></td>
</tr>
<tr>
<td>12 y.</td>
<td>NL/C</td>
<td></td>
</tr>
<tr>
<td>6 y.</td>
<td>NL/NL</td>
<td></td>
</tr>
<tr>
<td>4 y.</td>
<td>NL/NL</td>
<td></td>
</tr>
</tbody>
</table>

SNHL = sensorineural hearing loss
M = mixed hearing loss
C = conductive hearing loss
NL = normal hearing

Affected (COL1A1; c.1354-12G>A)
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)*

<table>
<thead>
<tr>
<th>Audiologic phenotype</th>
<th>C allele</th>
<th>T allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Normal hearing</td>
<td>18 (17.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>86 (82.7)</td>
<td>5 (100.0)</td>
</tr>
<tr>
<td>Conductive/mixed hearing loss</td>
<td>70 (67.3)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>Pure sensorineural hearing loss</td>
<td>16 (15.4)</td>
<td>2 (40.0)</td>
</tr>
</tbody>
</table>

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

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
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