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# Otosclerosis

-Basic science and clinical significance-

-IFOS World Course 2019-

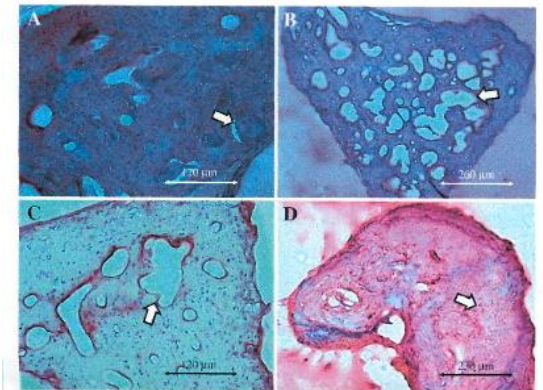
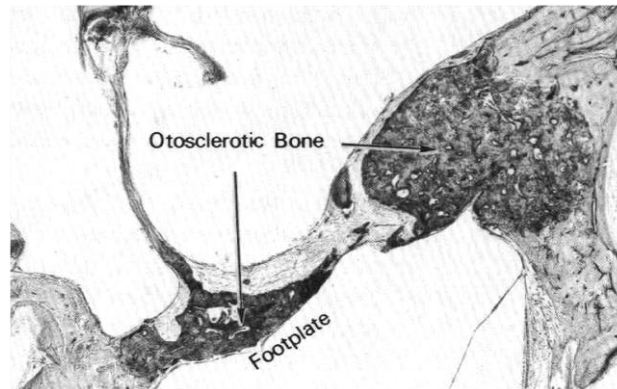
**Department of Otolaryngology**

**Keio University**  
**K Ogawa MD, PhD**



# otosclerosis

- **Otosclerosis is caused by a single or multiple spongifying lesions beginning in the endocochlear layer of the capsular bone.**
- **Characteristic pathological finding is otospongiosis in which bone formation and bone resorption are both present.**
- **Incomplete autosomal dominant transmission with low penetrance (40%).**





# Etiology

## (1) genetics

- **The incidence differs among races suggesting that the genetic factor may be involved in the etiology (Incomplete autosomal dominant transmission).**

<i>Gene</i>	Report	Location	Function
<i>OTSC1</i>	Tomek et al. 1998	15p25-q26	unknown
<i>OTSC2</i>	Van Den Bogaert et al. 2001	7q34-q36	unknown
<i>OTSC3</i>	Chen et al. 2007	6p22.3-p21.2	unknown
<i>OTSC4</i>	Brownstein et al. 2006	16q21-q23.2	unknown
<i>OTSC5</i>	Van Den Bogaert et al. 2001	3q22-q24	unknown
<i>OTSC6</i>	N/A	unknown	unknown
<i>OTSC7</i>	Thys et al. 2007	6q13-q16.1	unknown
<i>OTSC8</i>	Bel Haji Ali et al. 2008	9p13.1-9q21.11	unknown
<i>CD46</i>	Karosi et al. 2008	1q32	CD46/measles virus receptor
<i>TGF-beta1</i>	Thys et al. 2007	19q13.2: 19q13.1	TGF-beta1
<i>COL1A1</i>	McKenna et al. 1998	17q21.33	Type I collagen
<i>BMP2</i>	Schrauwen et al. 2008	20p12	Bone morphogenetic protein
<i>BMP4</i>	Schrauwen et al. 2008	14q22-q23	Bone morphogenetic protein



# Etiology

## (2) latent measles infection

- 1981 Paget's disease=paramyxovirus infection
- 1986 McKenna : measles nucleocapsid
- 1989 Arnold : paramyxovirus IgG in footplate
  - measles, rubella, mumps (?)
- 1994 Niedermeyer : measles virus RNA
- 1996 Arnold : measles in perilymph
- 2000 Niedermeyer : 83% (+)
- 2000 Grayeli : no evidence of measles virus infection (n=35)
- 2004 Karosi: footplate 20/34 (+)
- 2007 Karosi: measles virus receptor (CD46)
- 2011 Komune: no evidence of measles virus infection in Japanese otosclerosis



# Pathophysiology of otosclerosis

**Genetics : COL1A1、 BMP2,4 polymorphism  
OTSC1~8 gene、 alternative splicing of CD46**

**Measles virus**

**Inflammation**

**TNF $\alpha$**

**TGF $\beta$  1**

**IL-1、 IL-6**

**OPG**

**RANK、 RANKL**

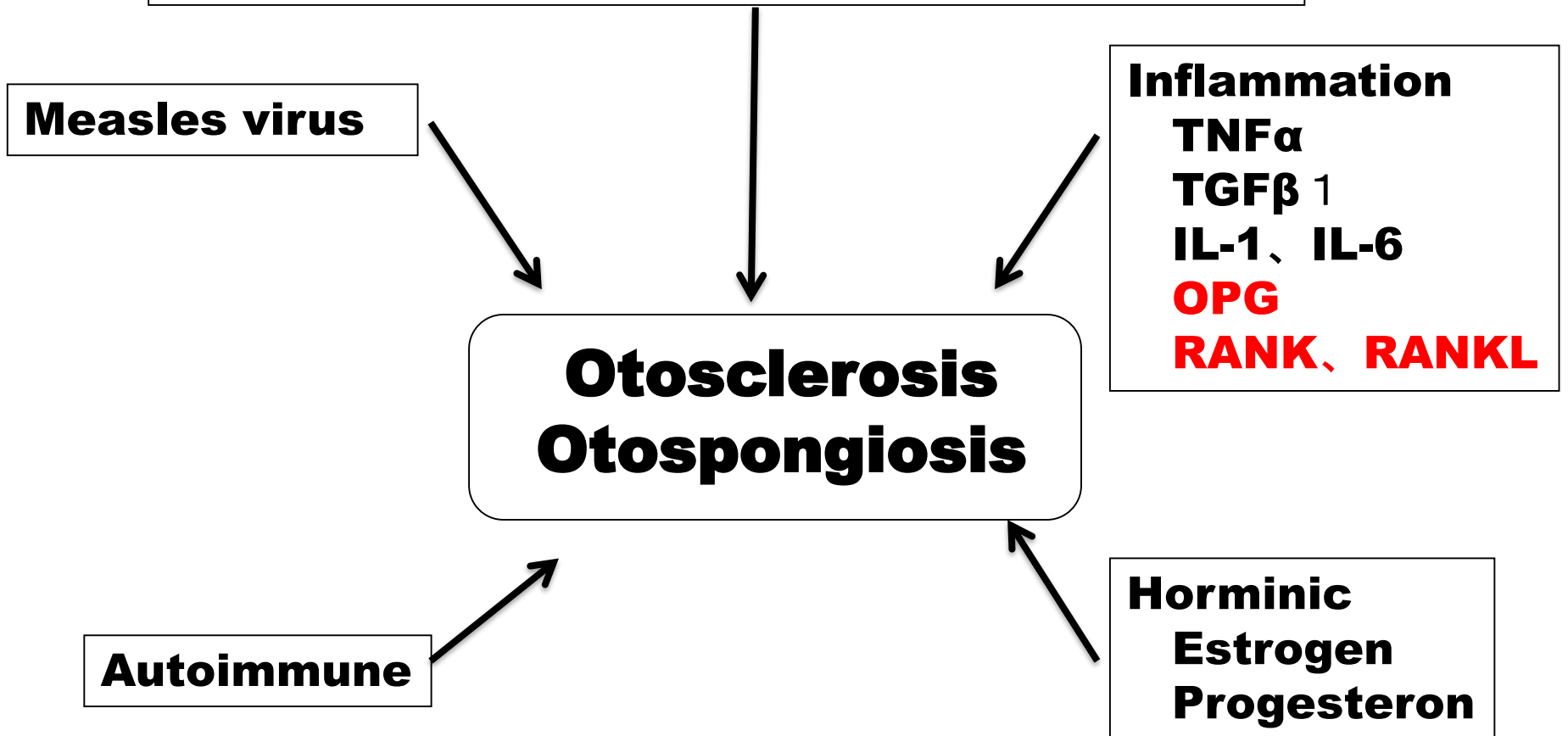
**Otosclerosis  
Otospongiosis**

**Autoimmune**

**Horminic**

**Estrogen**

**Progesteron**





# Animal model of otosclerosis

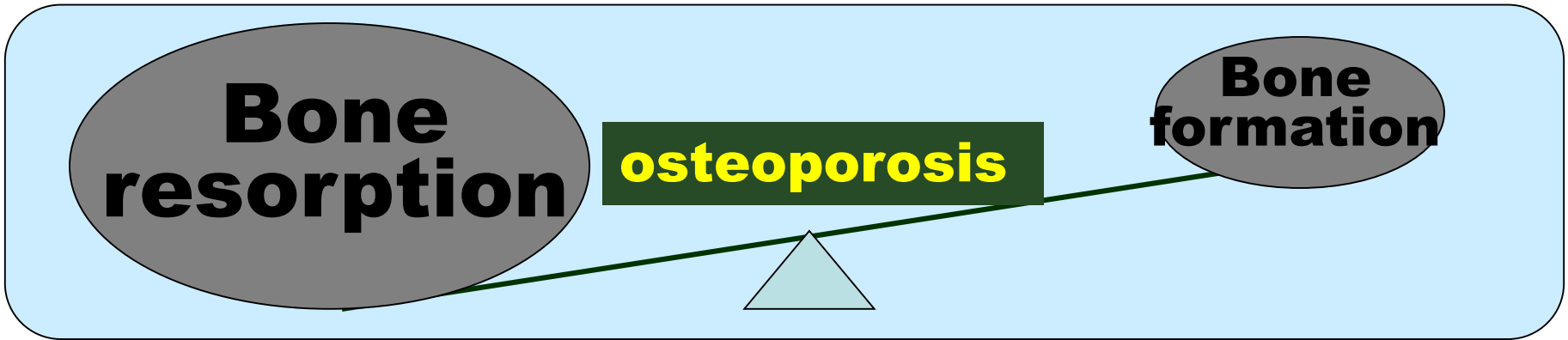
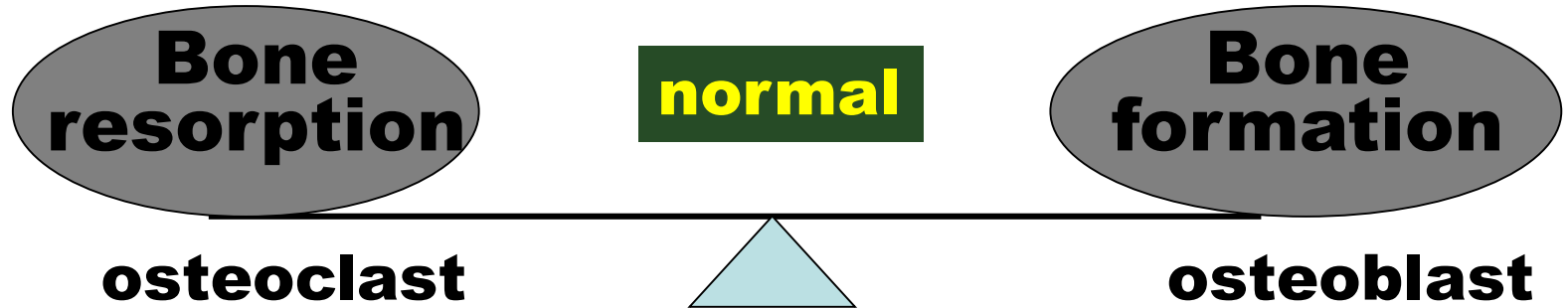
- **Morphological changes in the ossicles and changes in hearing in *opg* knock out mouse**
- ***opg* KO (-/-), hetero (+/-), wild (+/+) mice  
6,10,15 week-old ♀**

- 1) **Morphology of the ossicles A) macroscopic, B) microscopic (paraffin embedded sections)**
- 2) **TRAP activity (tartrate-resistant acid phosphate) which suggests osteoclast activity.**
- 3) **μCT analysis (10 week-old ♀)  
malleal and tibial cortical thickening**
- 4) **Acoustic brain stem response (ABR)  
2, 4, 12, 20 kHz**

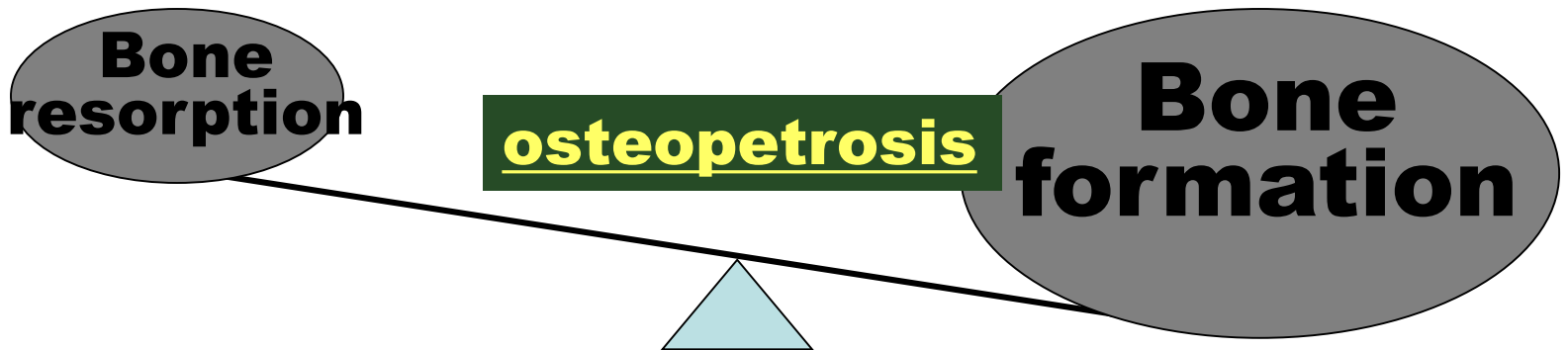




# Bone remodeling

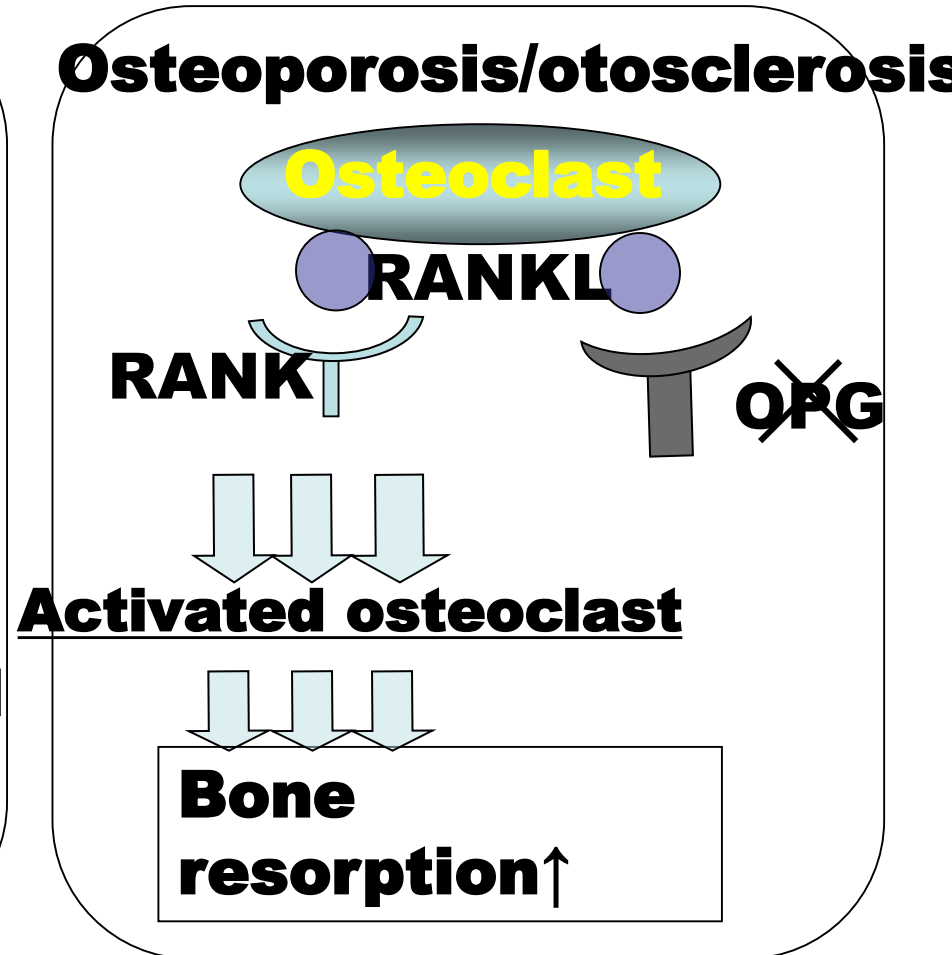
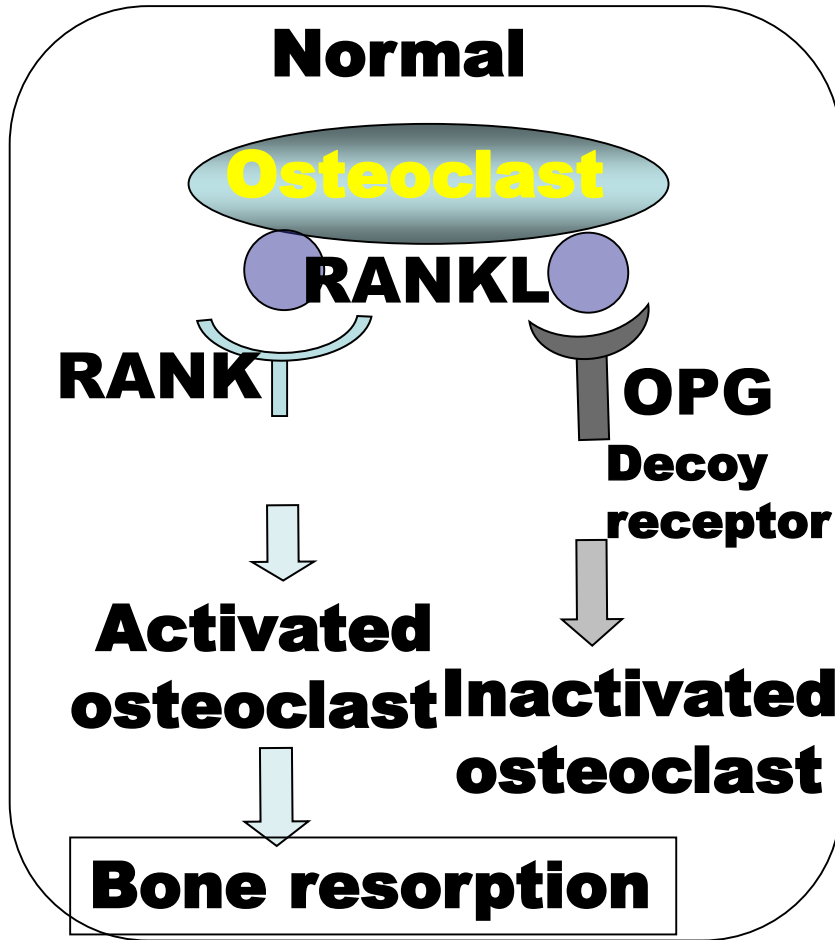


**When bone resorption is up-regulated, the bone will become osteoporotic.**





# Mechanism of bone resorption



**RANKL: Receptor Activator NFκB Ligand**

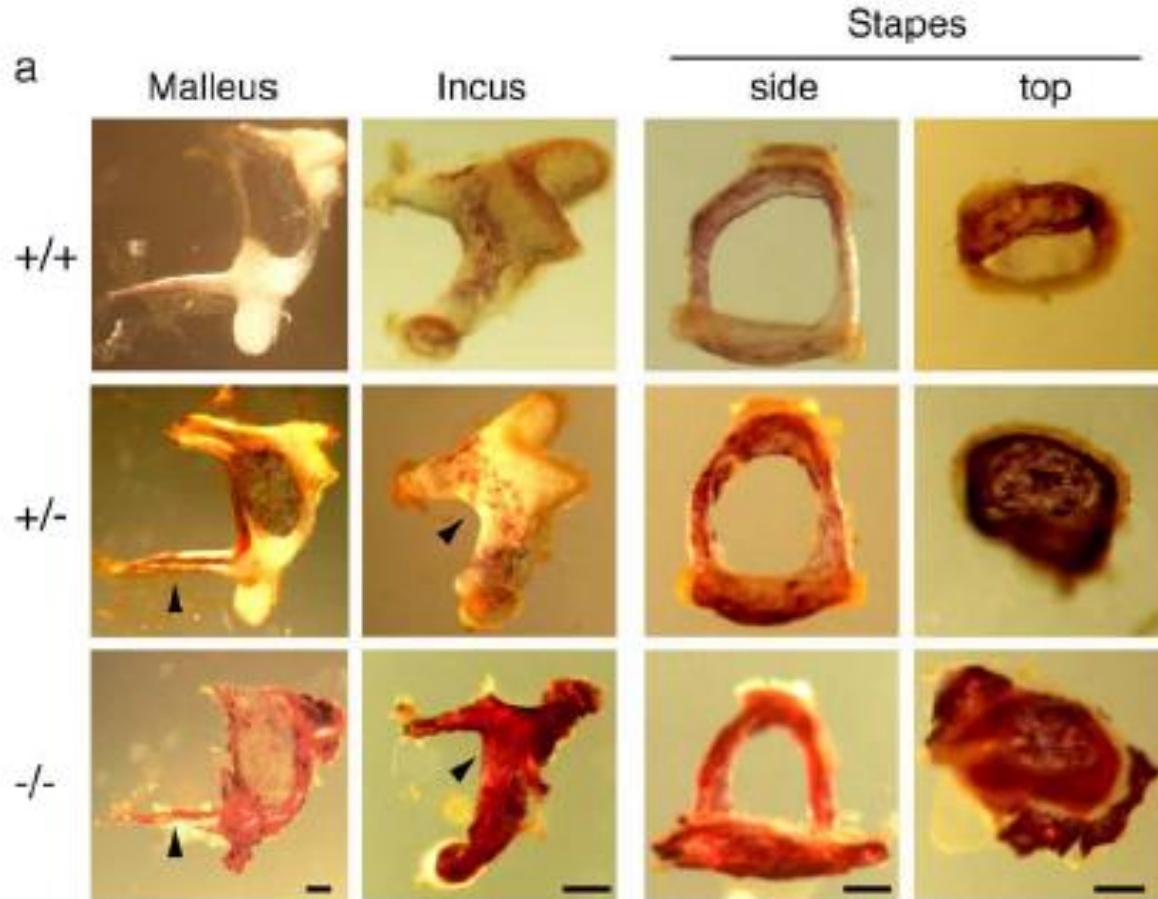
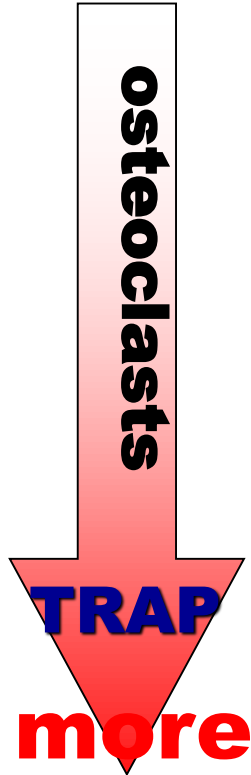
**RANK: Receptor Activator NFκB**

**OPG: Osteoprotegerin**



# Ossicles and osteoclasts

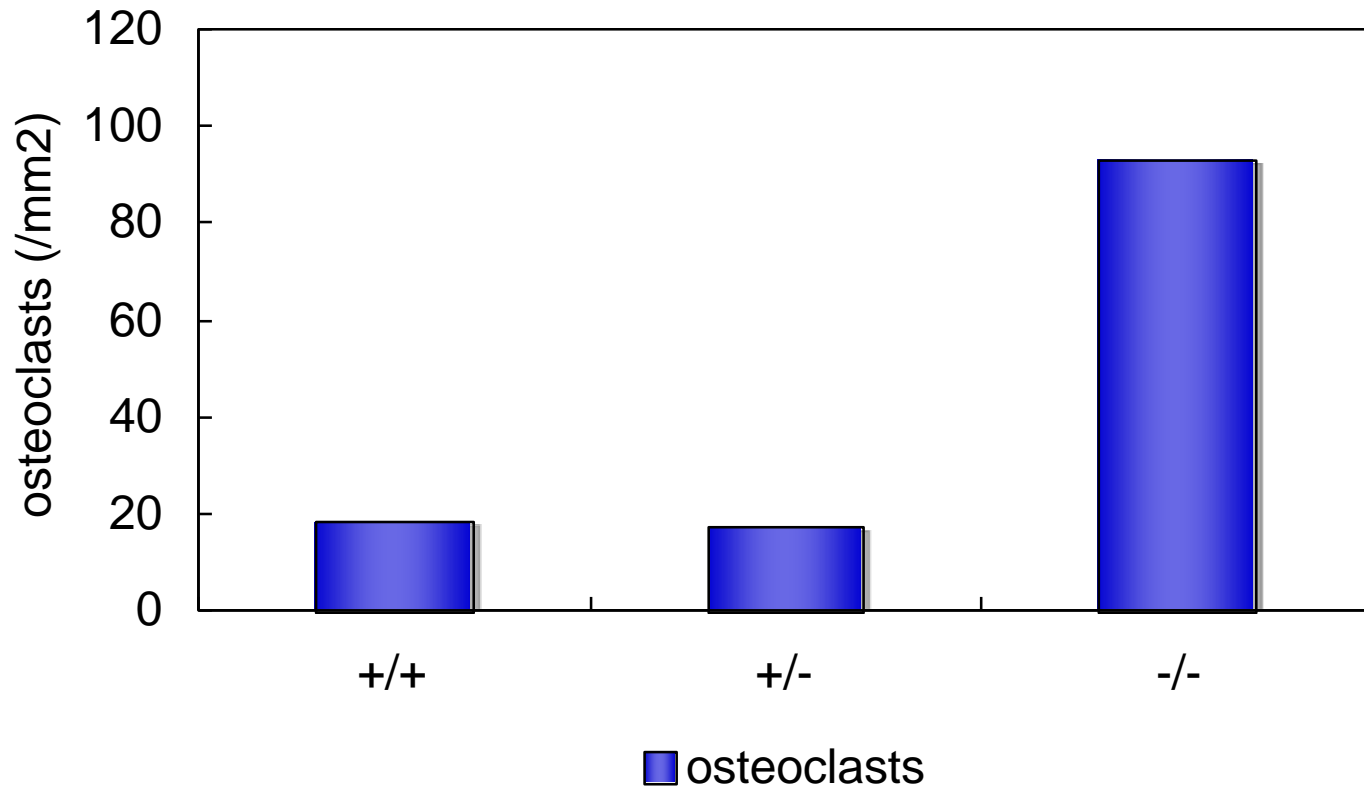
less



Red staining suggests the higher activity of osteoclast. From these results of TRAP staining, we can clearly observe the higher activity of osteoclast in the opg KO mouse.



# Number of osteoclasts

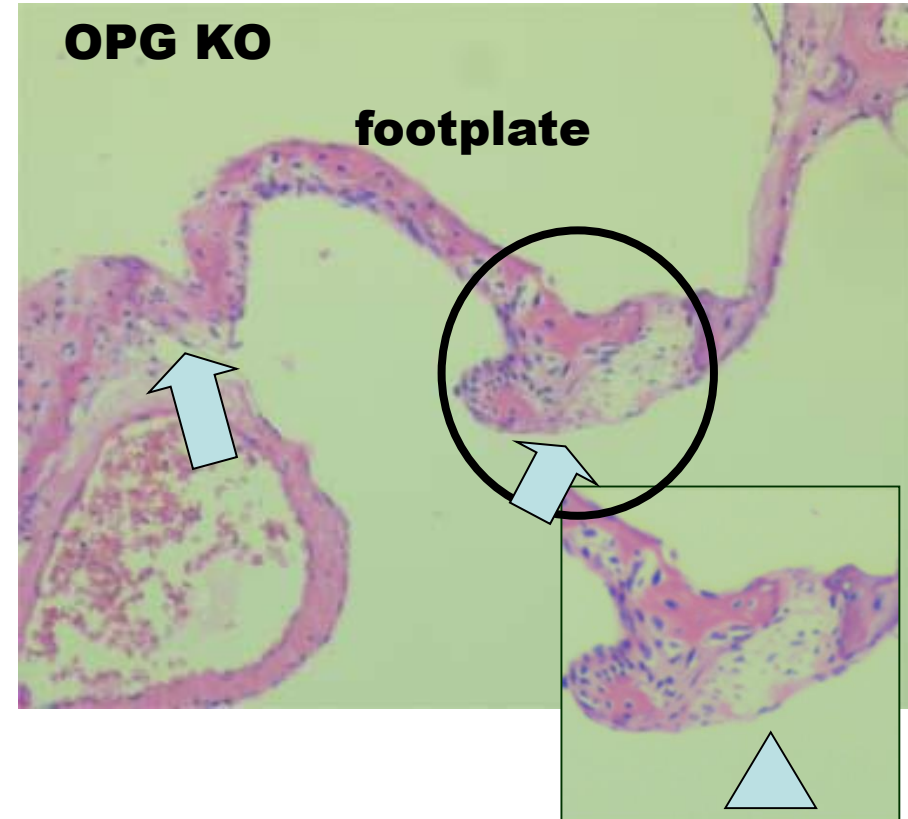
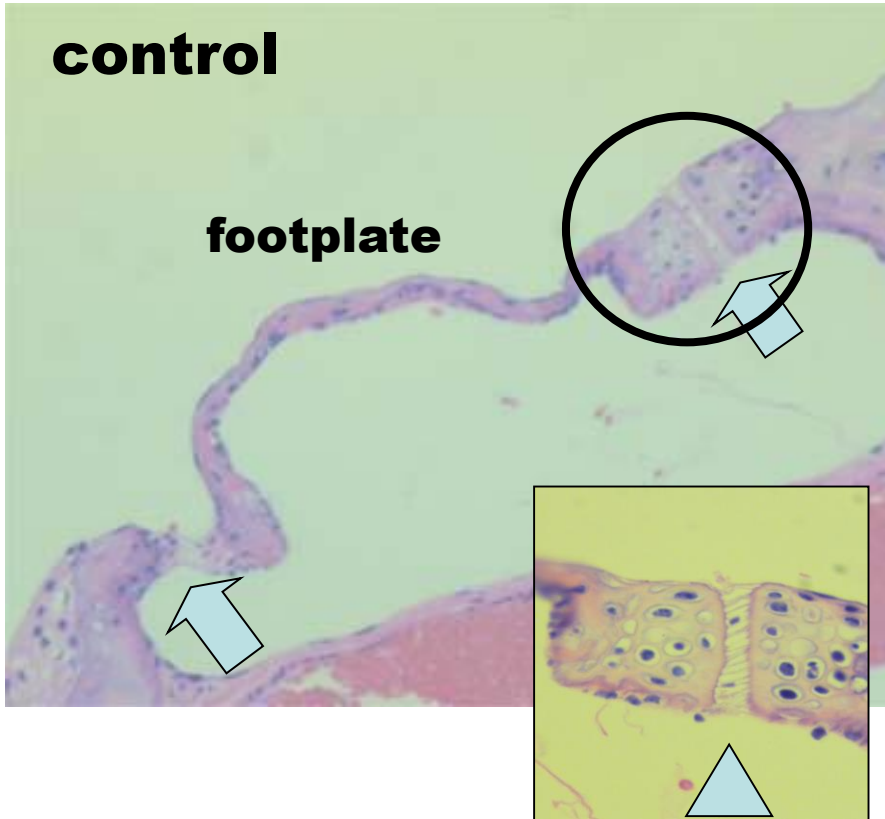


**The number of osteoclasts increased 6~7 times higher in opg KO mice than in the controls.**



# Stapes

## H&E staining

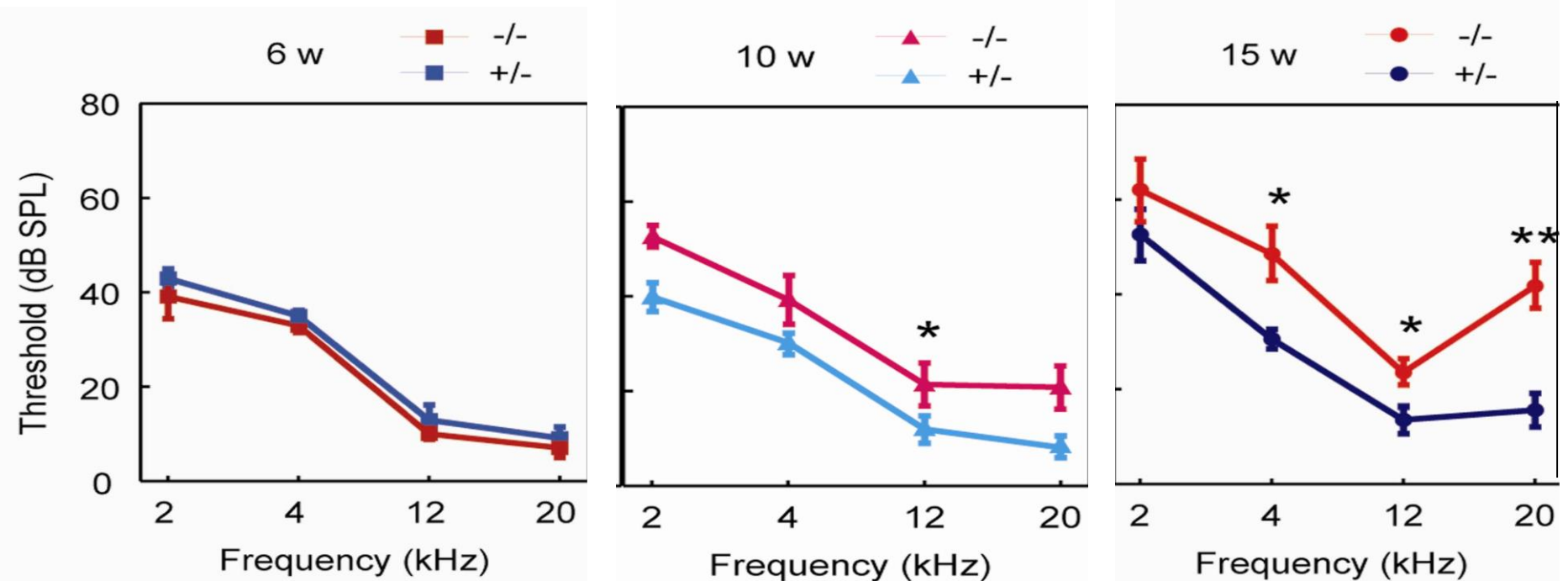


**in *Opg* KO mice, no ligament exists and the junction is replaced with bone tissue which fuses the stapes and the otic capsule.**

**These changes are similar to the changes in otosclerosis.**

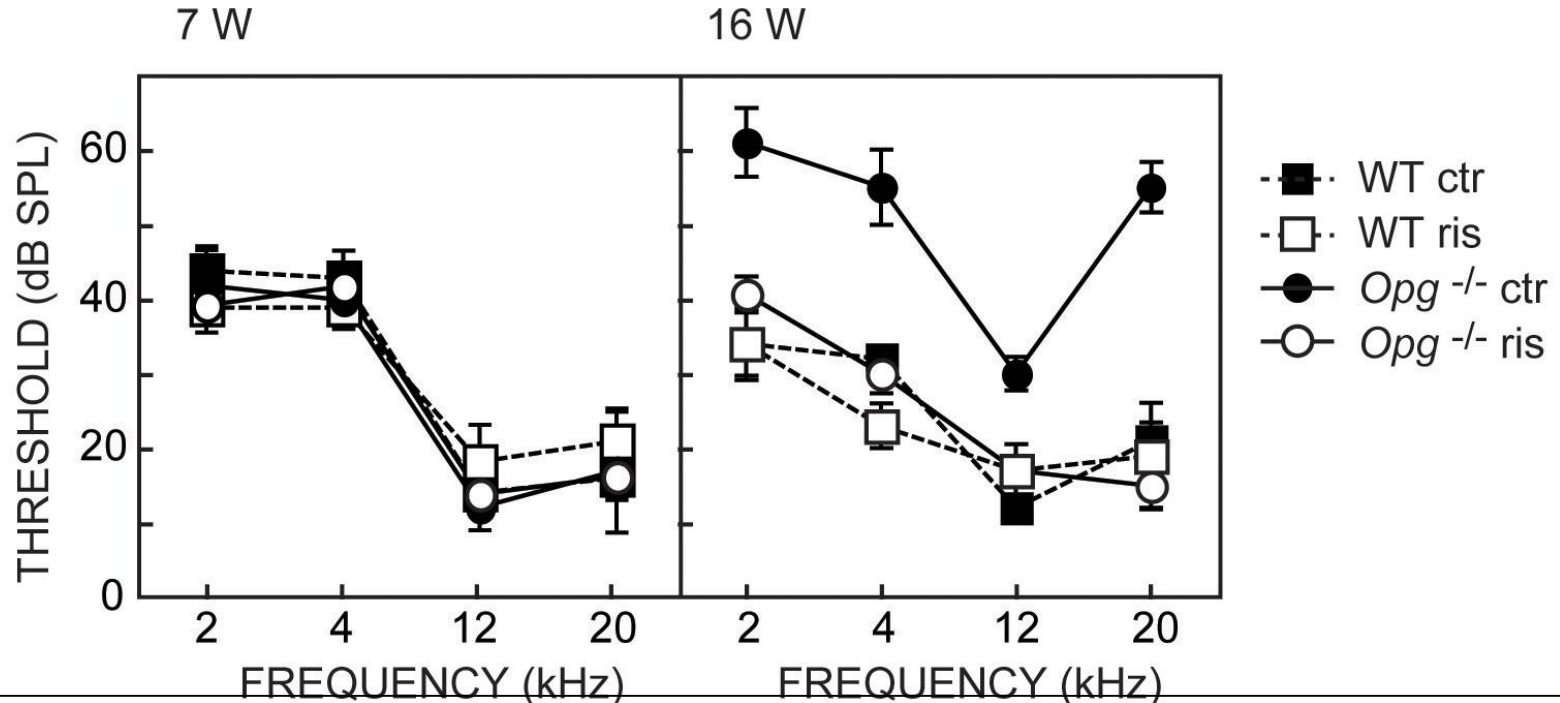


# Hearing threshold increased as age



**These data suggest that osteoporotic changes result in progressive hearing loss, which is similar to hearing loss in otosclerosis.**

# Sodium risedronate can prevent hearing loss

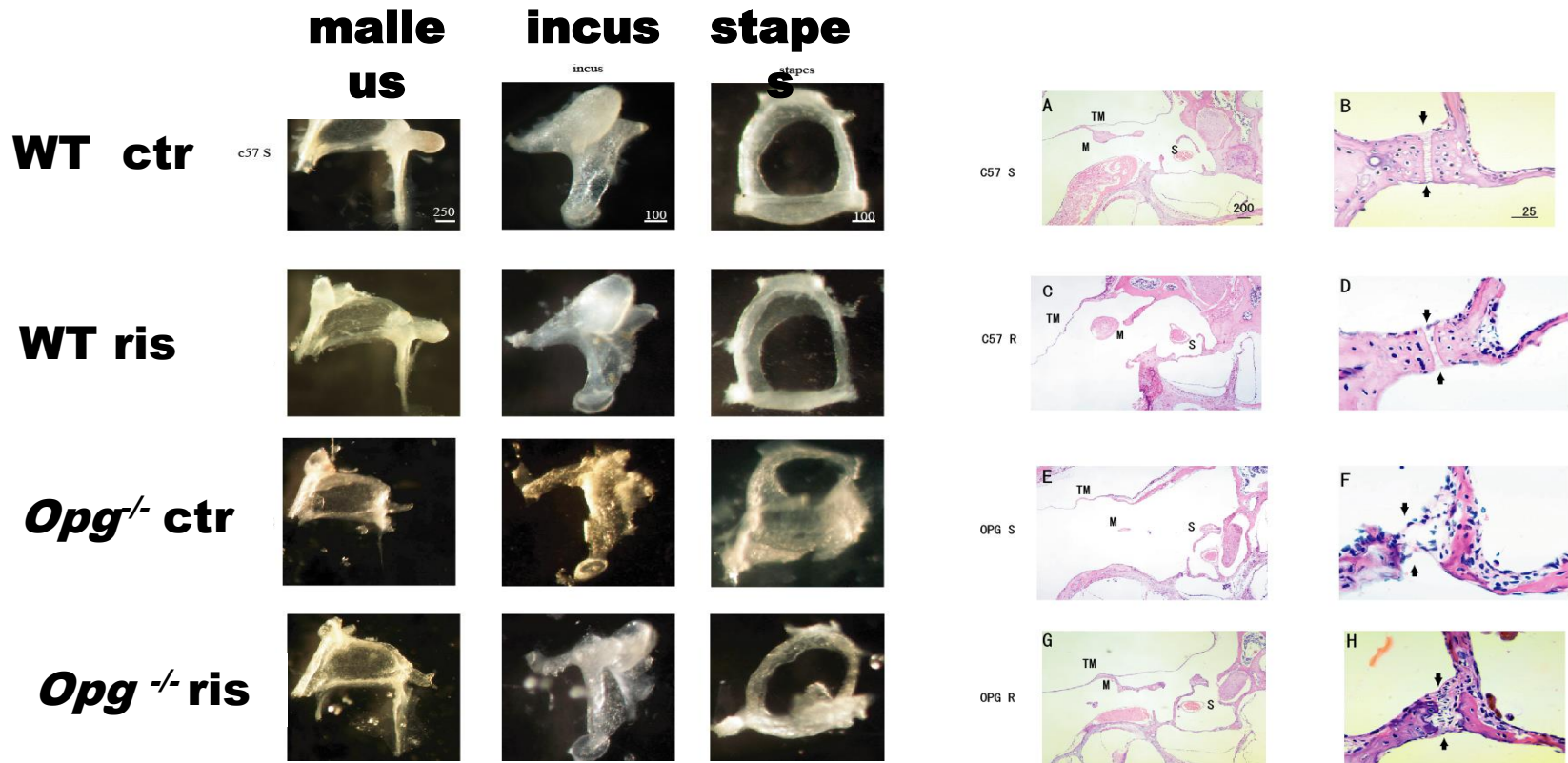


**Bisphosphonate (sodium risedronate): anti-osteoporosis medicine**

- Bind to bone mineral surface and uptake into osteoclasts
- Inhibit farnesyl diphosphate synthase, a key enzyme of the mevalonate pathway



# Sodium risedronate prevents the morphological changes in ossicles



**Risedronate treatment prevented bone erosion of malleus, incus and stapes, and the stapedia-cochlear junction**



# Can risedronate prevent progressive hearing loss ?

**Subjects: Woman (Otosclerosis + Osteoporosis)**

**Risedronate 35mg/wk  
10 ears**

**SERM 60mg/day  
10 ears**

**Follow-up (3yrs)  
Audiogram, TG  
Bone density**

**Selective  
estrogen  
receptor  
modulators**

**Compared to the historical control**





# Bone remodeling

**Bone  
resorption**

**normal**

**Bone  
formation**

**osteoclast**

**osteoblast**

**Bone  
resorption**

**osteoporosis**

**Bone  
formation**

**Bone  
resorption**

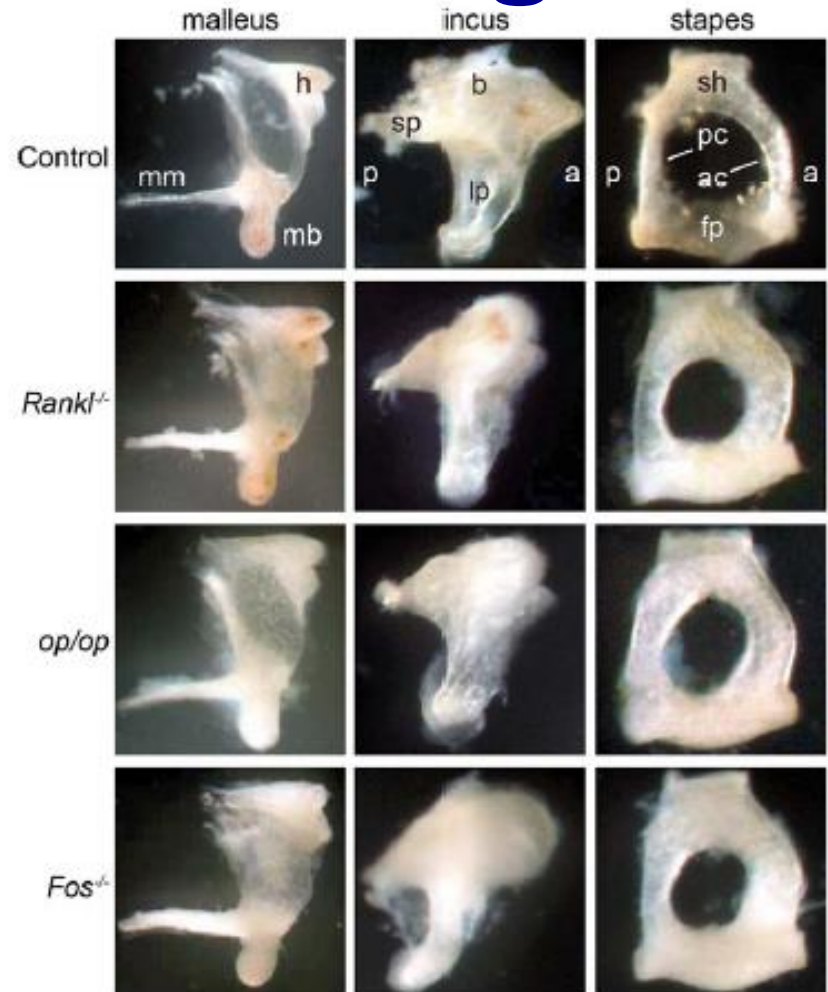
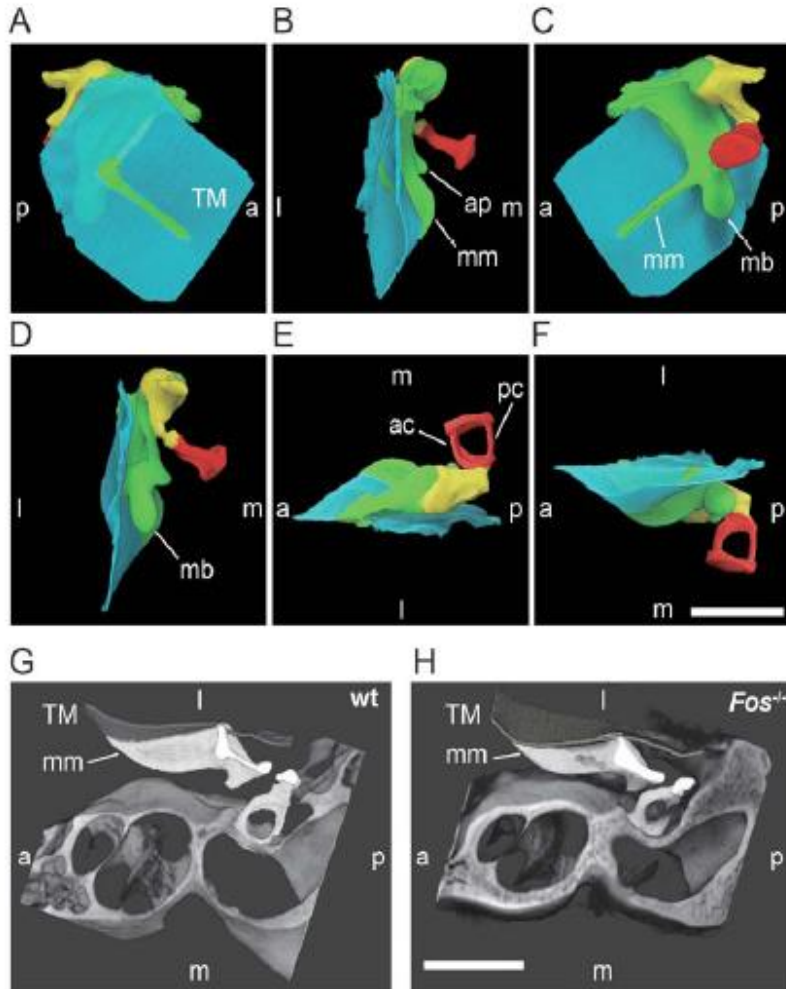
**osteopetrosis**

**Bone  
formation**

**When bone formation is up-regulated, the bone will become osteopetrotic.**



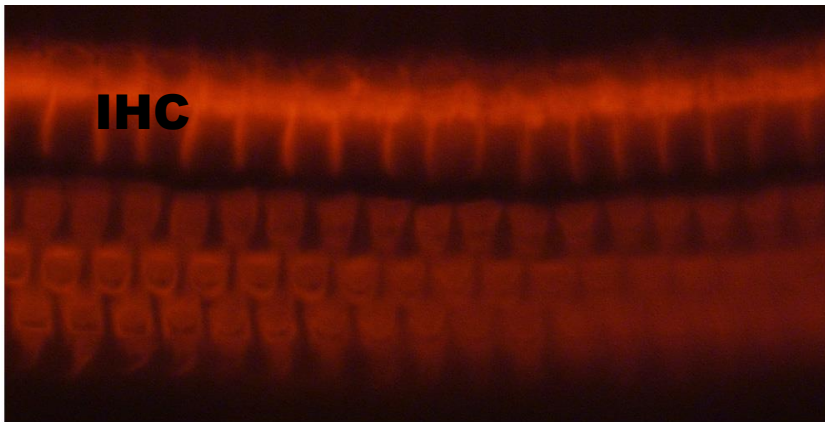
# Osteopetrotic ossicles show aberrant thickening





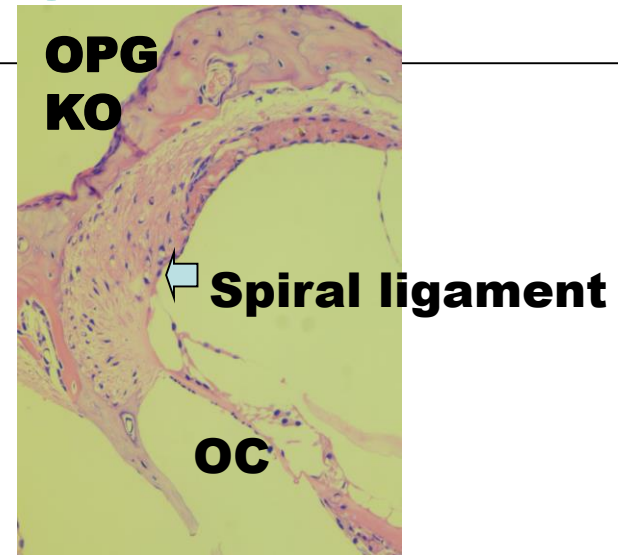
# Summary

- ***opg* KO mouse shows progressive hearing loss caused by ossicular abnormality such as stapedial fixation.**
- **OPG may be a key factor of the etiology not only of Paget disease, but also of osteoporosis and otosclerosis.**
- **OPG is a protective factor against hearing loss caused by bone resorption.**
- **Risedronate may prevent progressive hearing loss.**
- **OPG is found in the perilymph (Zehnder 2005).**
- **Further study will be needed to figure out the role of OPG in the cochlea.**



OHC

OPG KO





# Clinical study

## “How to treat otosclerosis?”

**454 cases (600 ears) who underwent stapedectomy using an apatite ceramic implant (Apaceram-C) under microscope (+11 ears by TEES)**

### **(1) diagnosis**

**audiogram and tympanogram  
progression of hearing loss  
prevention of hearing loss**

### **(2) treatment**

**surgical results (hearing, tinnitus, ear fullness)  
long-term prognosis**



# Subjects

**600 surgically proven otosclerosis ears who underwent stapedectomy using an apatite ceramic implant.**

## ■ age

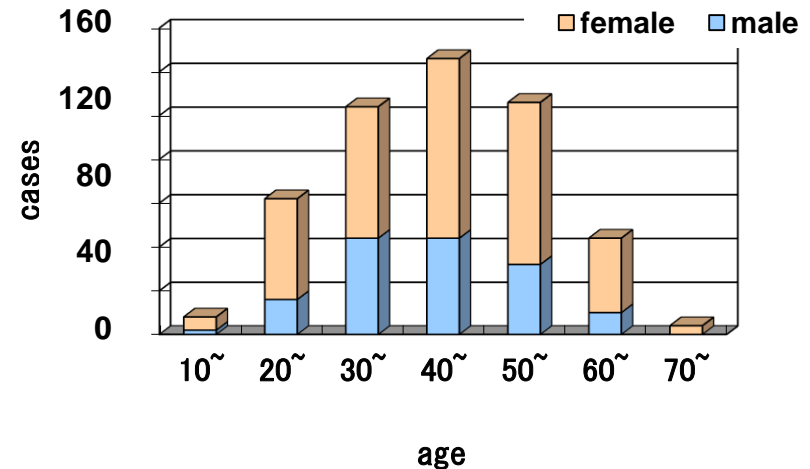
- 10~77 ( $43 \pm 13$ ) year-old

## ■ sex

- male: 146 (33%)
- female: 308 (67%)

## ■ laterality

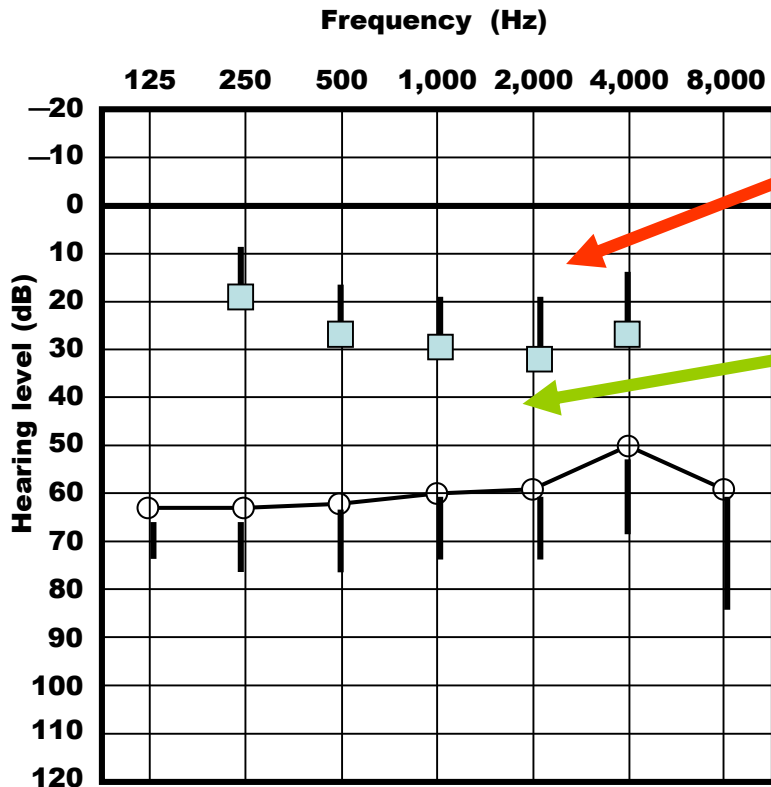
- unilateral: 98 (22%)
- bilateral: 356 (78%)



**(1) audiogram and tympanogram**

**(2) progression of hearing loss**

# Audiogram and tympanogram



**Carhart notch**

**$32.0 \pm 12.3\text{dB}$**

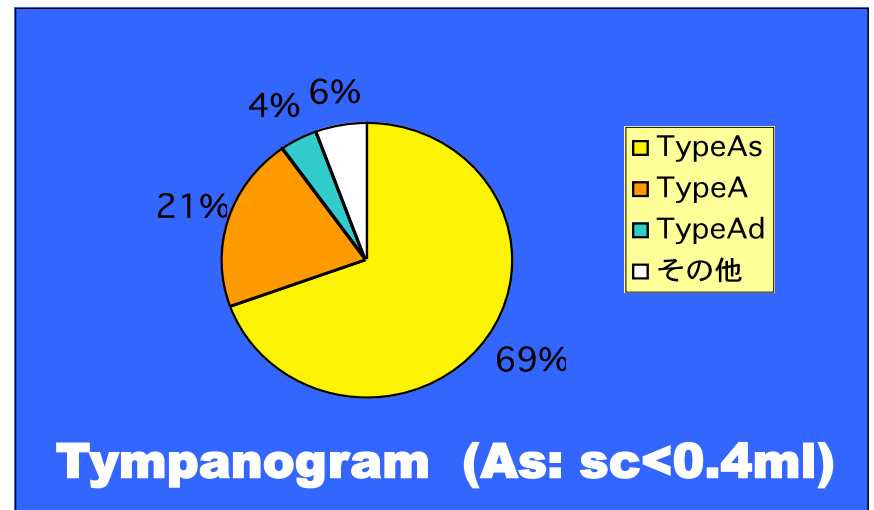
**(postop  $27.3 \pm 12.6\text{dB}$ )**

**5dB elevated at 1 and 4kHz**

**228 ears (38%)**

**Stiffness curve**

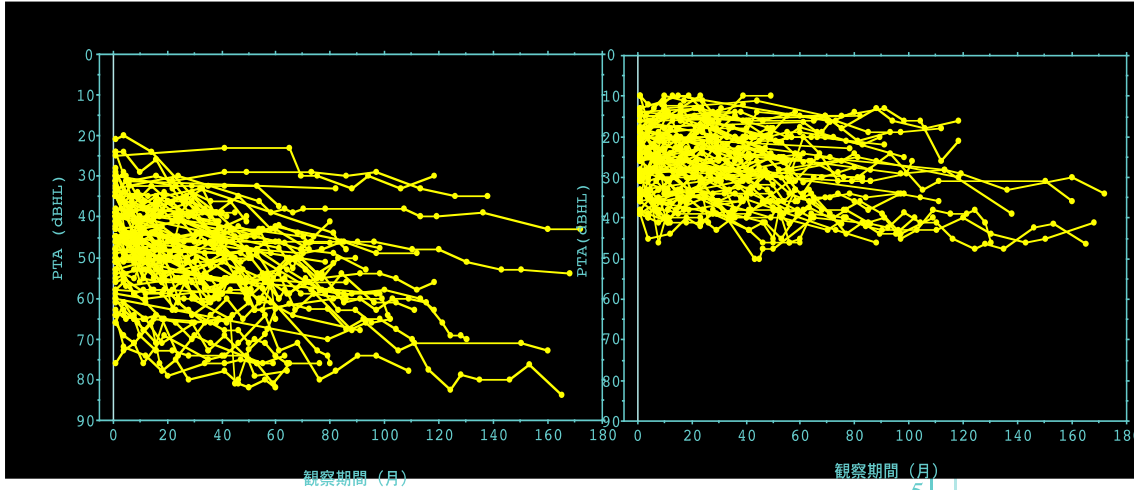
**$10.1 \pm 14.3\text{dB}$**





# Progression of hearing loss

Ears whose hearing loss could be observed more than 3 years.



**\* p<0.05**

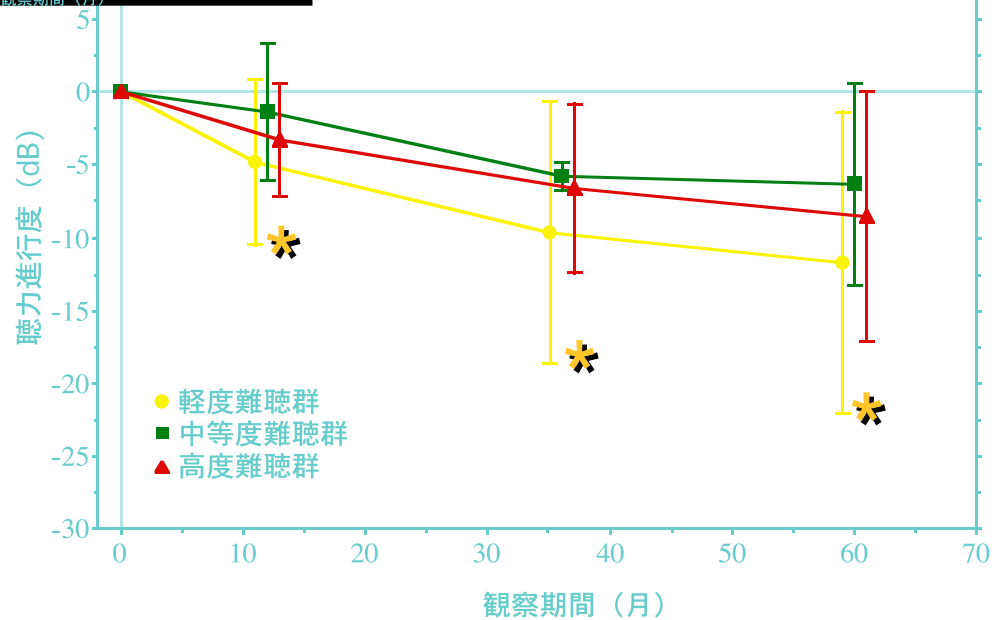
## Rate (dB/year)

**Mild (<40dB) 3.1 ± 2.2**

**Moderate (<60dB) 1.7 ± 1.7**

**Severe (>60dB) 1.7 ± 1.4**

**Total 2.3 ± 2.0**



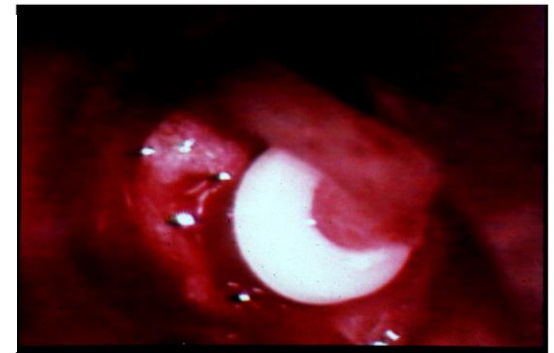
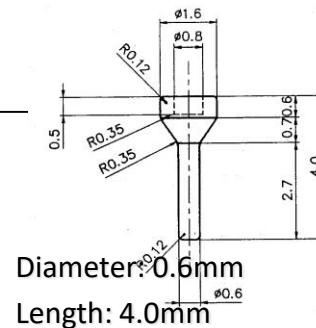




# Surgical methods using Apa-C

## Problems in Teflon-wire pistons

- **bio-compatibility**
- **MRI compatibility (3.0T and 4.7T)**
- **slippage**
- **necrosis of incudal long process**
- **perilymphatic fistula**



**bio-compatible apatite ceramic**

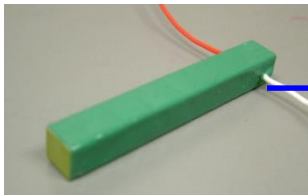




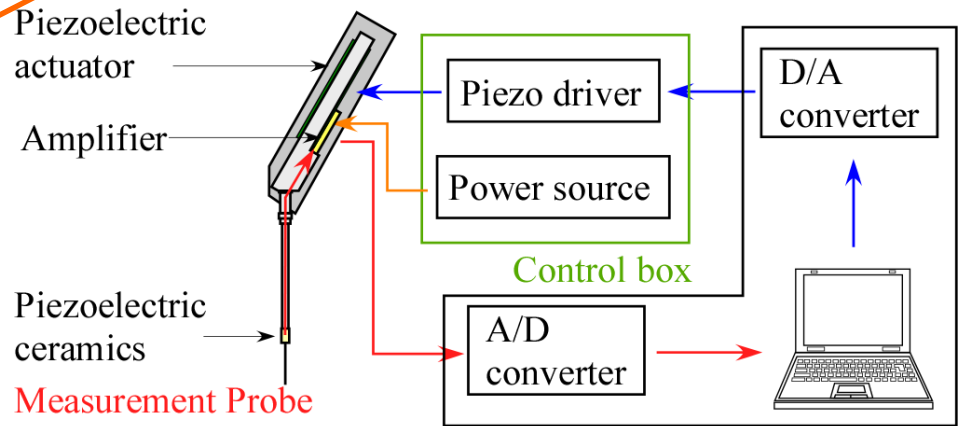
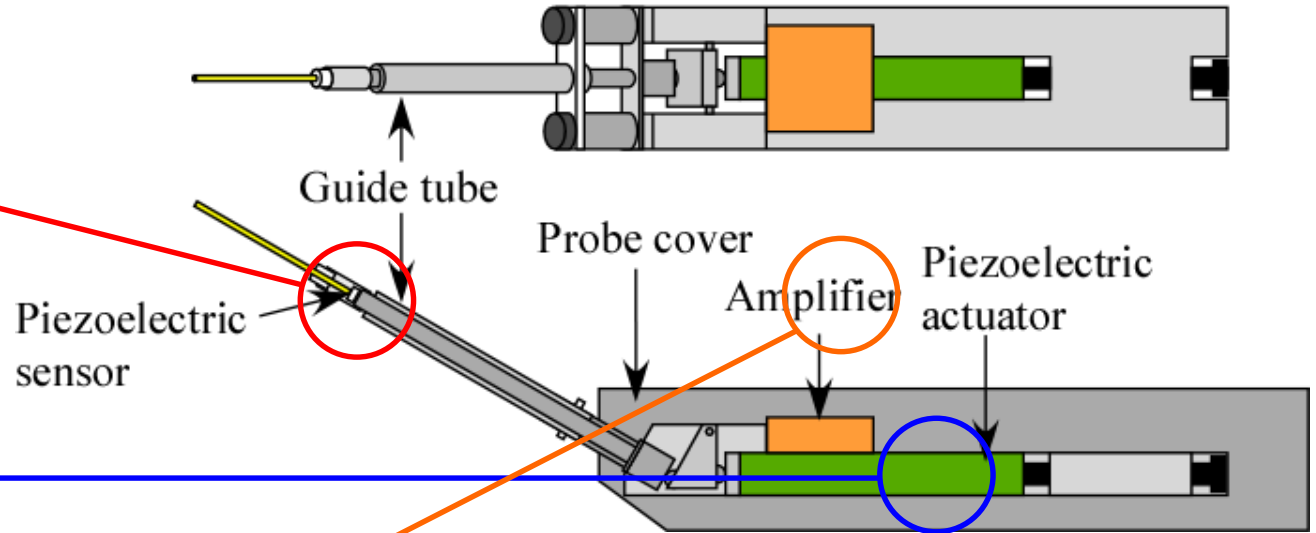
# Intraoperative measurement



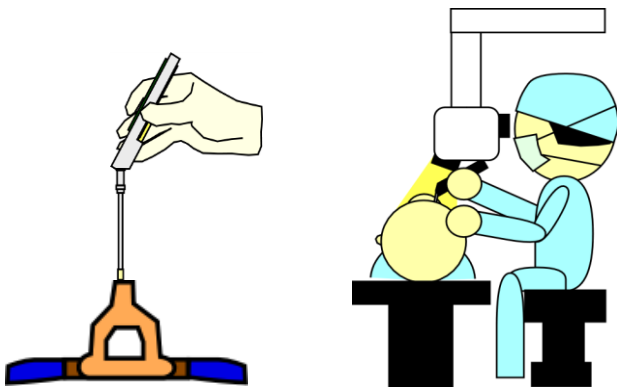
f2x1 [mm]



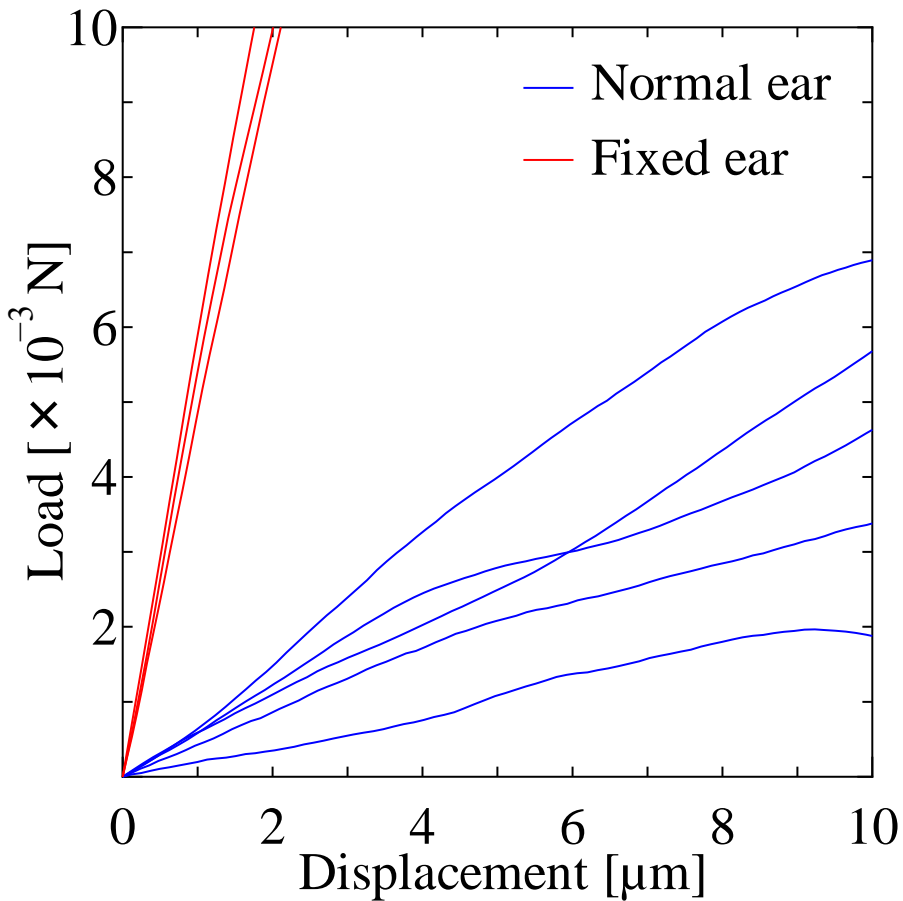
5x5x40 [mm]



ossicular mobility tester



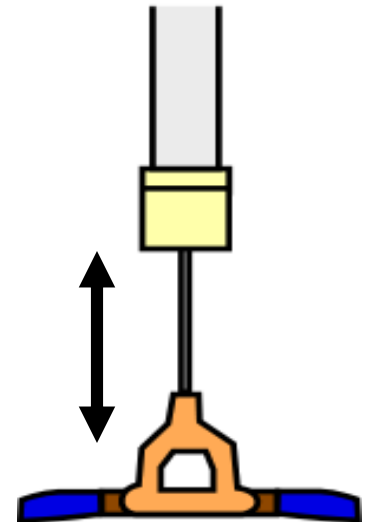
# Stapedial fixation



Compliance  
(Mobility)

Displacement

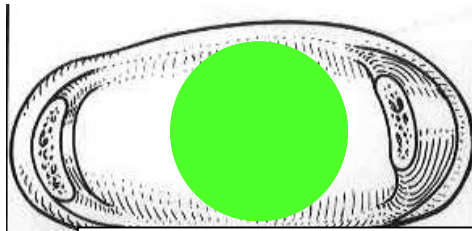
Load



$$\text{Compliance} = \frac{\text{Displacement}[\mu\text{ m}]}{\text{Load}[\text{N}]}$$

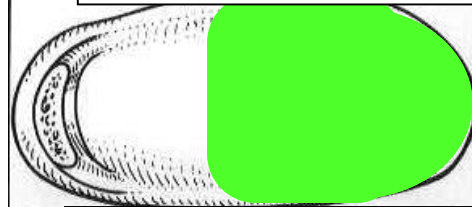


# SFS vs TS、 PS

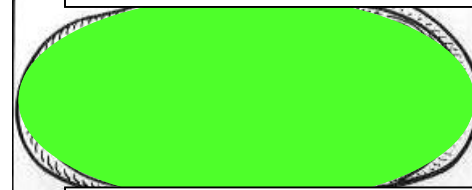


466 ears (78%)

Stapedotomy (SFS)



Partial Stapedotomy (PS)

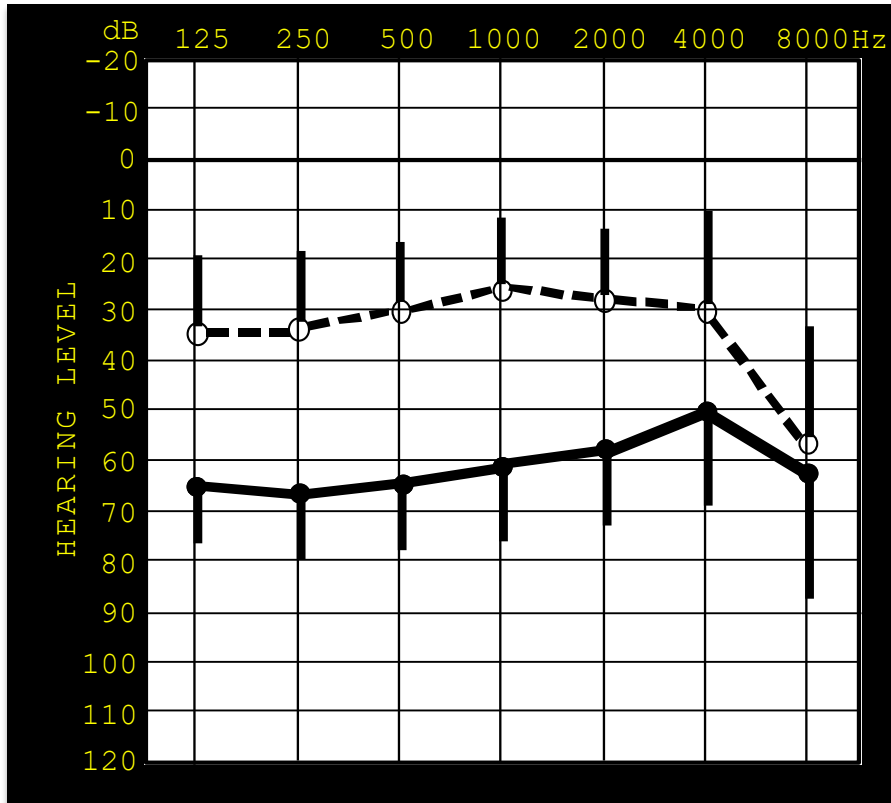


134 ears (22%)

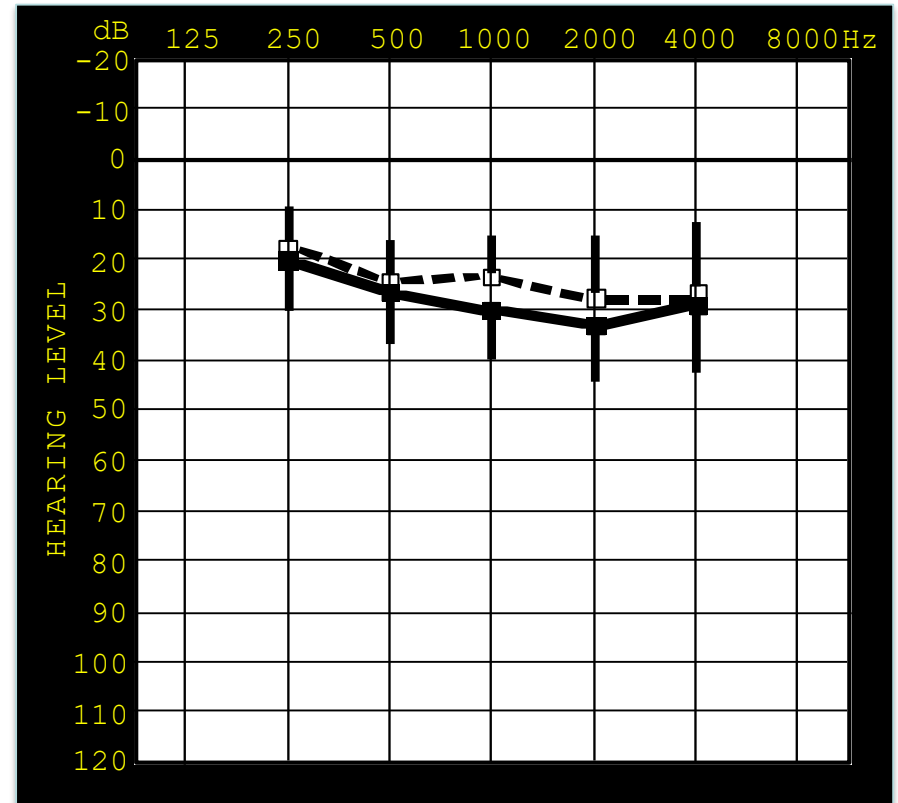
Total Stapedectomy (TS)



# Pre- and post-operative hearing ( $m \pm SD$ )



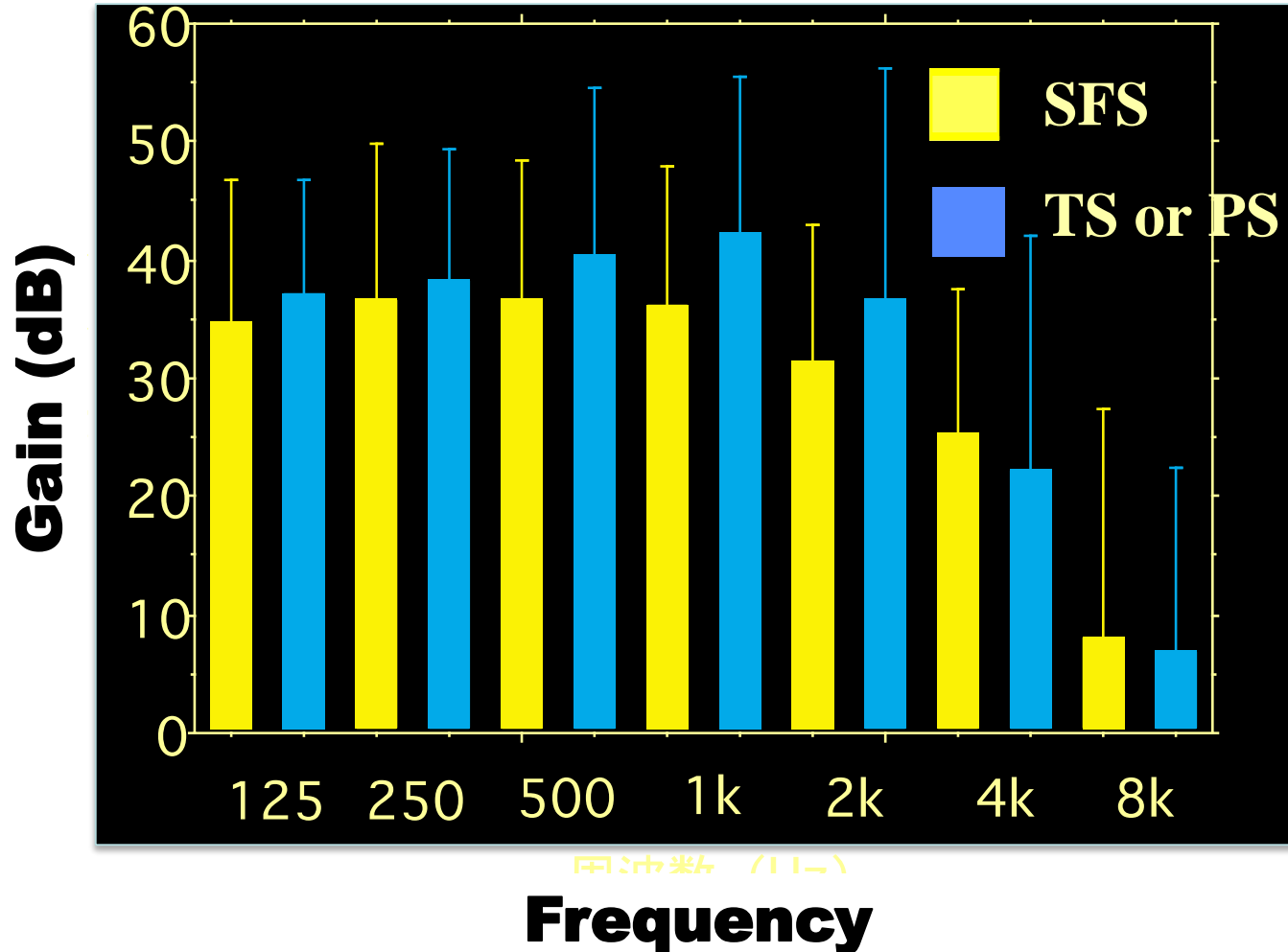
**air-conduction**



**bone-conduction**



# Hearing gain in each frequency





# Criteria for surgical results (the Japan Otological Society in 2000)

**1) Post-operative AB-Gap < 15dB**

**94.7% (568/600)**

**2) Hearing gain > 15 dB**

**90.0% (540/600)**

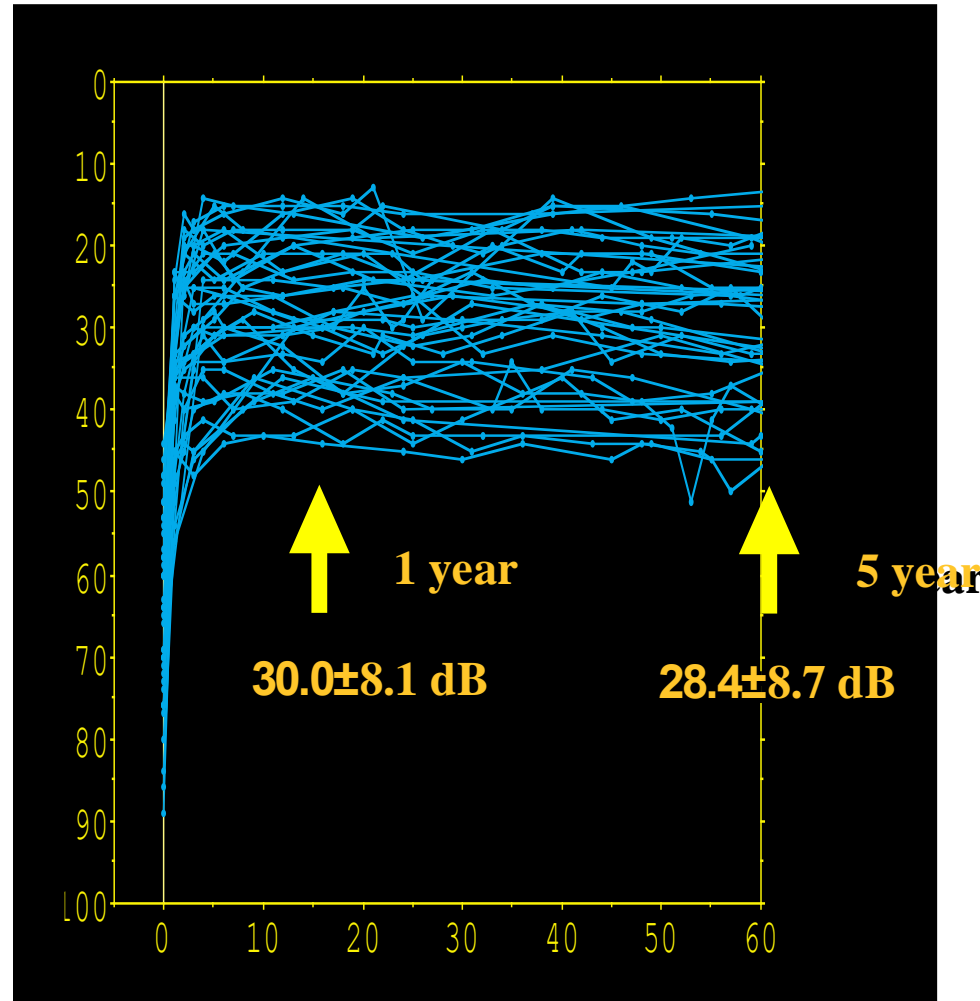
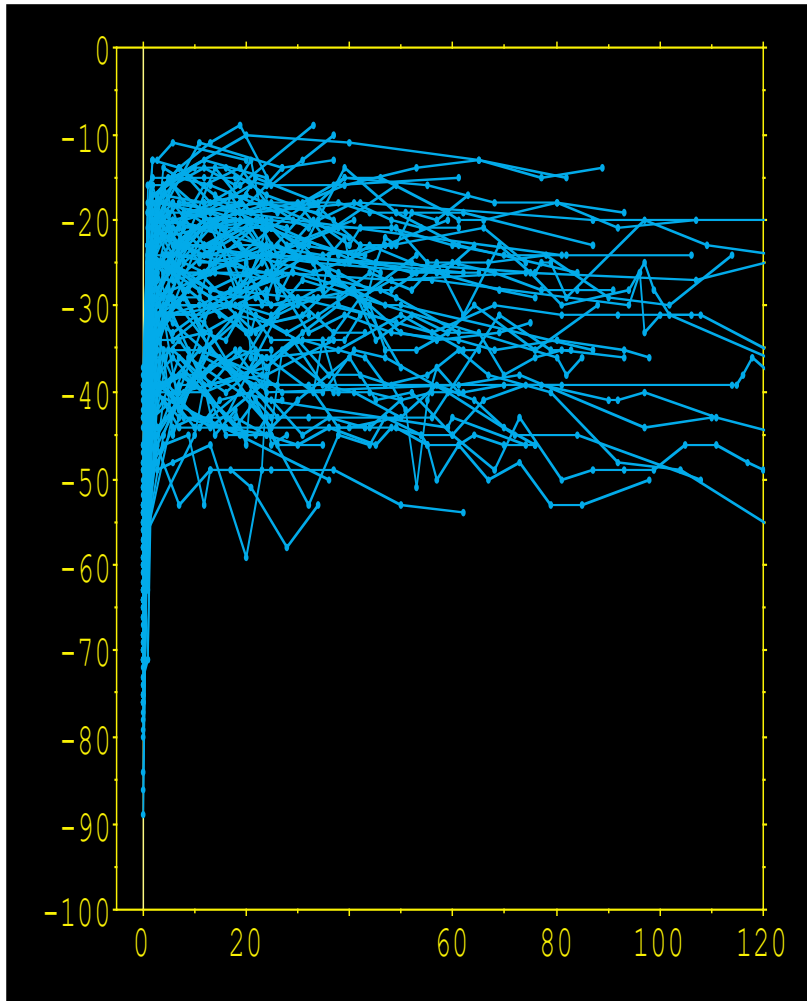
**3) Post-operative hearing level < 30dB**

**56.3% (338/600)**

**If cases who are fit to one of these criteria are successful, the successful rate is 98%.**



# Long-term prognosis of postoperative hearing





# Postoperative symptoms

## tinnitus (402 ears)

<b>disappeared</b>	<b>205 ears</b>	<b>(51.0%)</b>
<b>improved</b>	<b>128 ears</b>	<b>(31.8%)</b>
<b>unchanged</b>	<b>40 ears</b>	<b>(10.0%)</b>
<b>deteriorated</b>	<b>16 ears</b>	<b>( 7.2%)</b>

## ear fullness (194 ears)

<b>disappeared</b>	<b>120 ears</b>	<b>(61.9%)</b>
<b>improved</b>	<b>35 ears</b>	<b>(18.0%)</b>
<b>unchanged</b>	<b>21 ears</b>	<b>(10.8%)</b>
<b>deteriorated</b>	<b>4 ears</b>	<b>( 2.1%)</b>
<b>unknown</b>	<b>14 ears</b>	<b>( 7.2%)</b>





# Conclusion

- 1. We investigated the surgical results of stapedectomy using an apatite ceramic implant (Apa-C) in 600 otosclerosis under the microscope.**
- 2. Small fenestration stapedectomy was performed in 466 ears (78%), and total or partial stapedectomy in 134 ears (22%).**
- 3. Success rate was 98% in 600 ears, 98% in SFS and 97% in TS or PS.**
- 4. Improved hearing was maintained in the long-term postoperative observation, except 3 ear with cochlear otosclerosis.**
- 5. Tinnitus was improved in 83% of the ears, ear fullness was 80%.**