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UZA

Clinical and genetic aspects of otogenetics

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Belgium

Clinical and genetic aspects of otogenetics

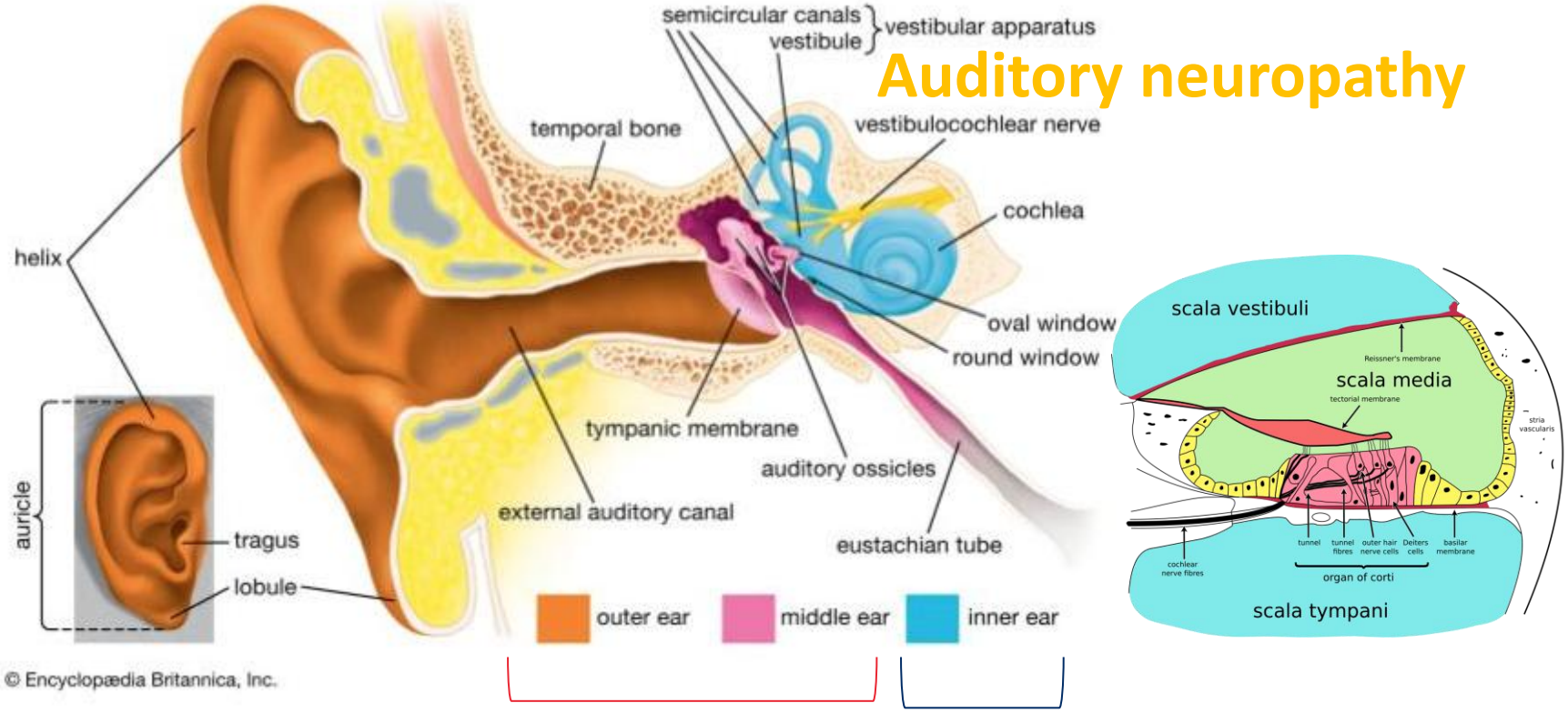
- General introduction
- Non-syndomic hearing loss
- Syndromic hearing loss

Clinical and genetic aspects of otogenetics

- **General introduction**
- Non-syndomic hearing loss
- Syndromic hearing loss

Hearing loss

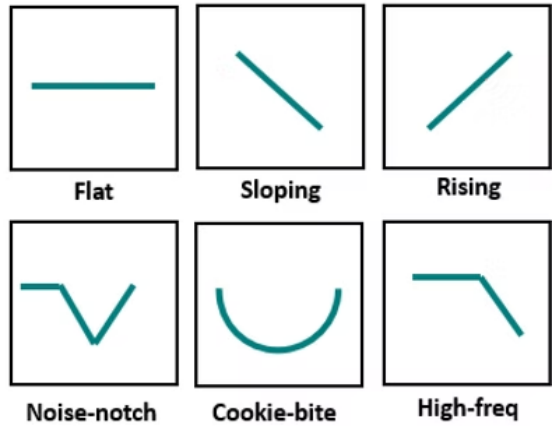
Severity	Hearing Threshold in dB
Slight	12-25 dB
Mild	26-40 dB
Moderate	41-60 dB
Moderately severe	61-70 dB
Severe	71-90 dB
Profound	>90 dB



Auditory neuropathy

Water dripping ~10dB
Conversation ~60dB

Audiogram configuration



Conductive

Perceptive/sensorineural

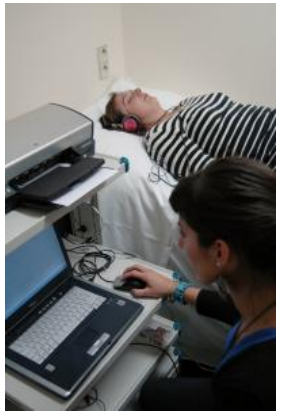
Mixed

Diagnostic tests

Algo: neonatal screening

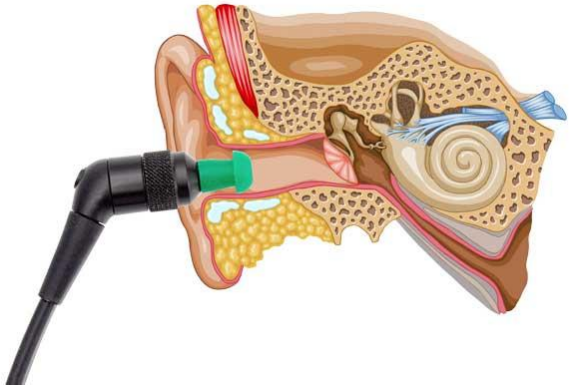
- 2-4 weeks
- Sleeping
- Measure brain activity after auditory stimulus
- Automatic interpretation
- Objective

Brainstem Evoked Response Audiometry (BERA)



- Measure brain activity after auditory stimulus
- Sleeping (esp. babies and infants)
- Manual interpretation
- Objective

Otoacoustic emissions



- Sounds generated by cochlea
- Spontaneous/evoked
- Objective
- Cave auditory neuropathy

Audiometry

- Subjective hearing test
- Conditioned orientation <2,5 years
- Instrumentation conditioned reflex 2,5-5 years
- Tonal >5 years

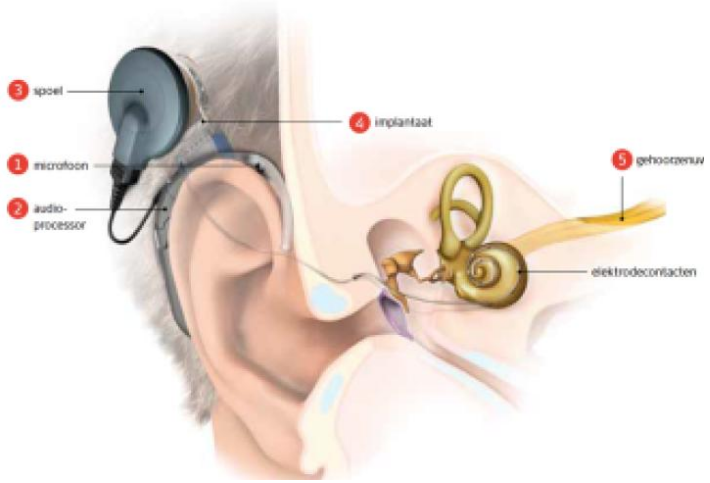
Tympanometry & vestibular testing

Treatment

Hearing aid

- Mild/moderate hearing loss
- Any age

Cochlear implant

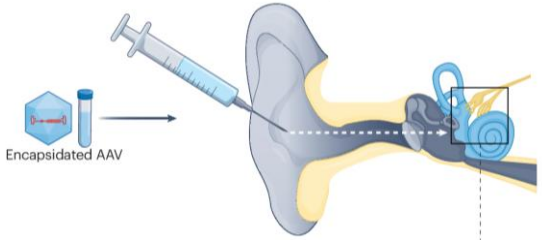


- Severe hearing loss
- ~6-12m

Auditory verbal therapy

- Optimise use of remaining hearing capacity
- Based on hearing nog eg lip reading

Gene therapy?

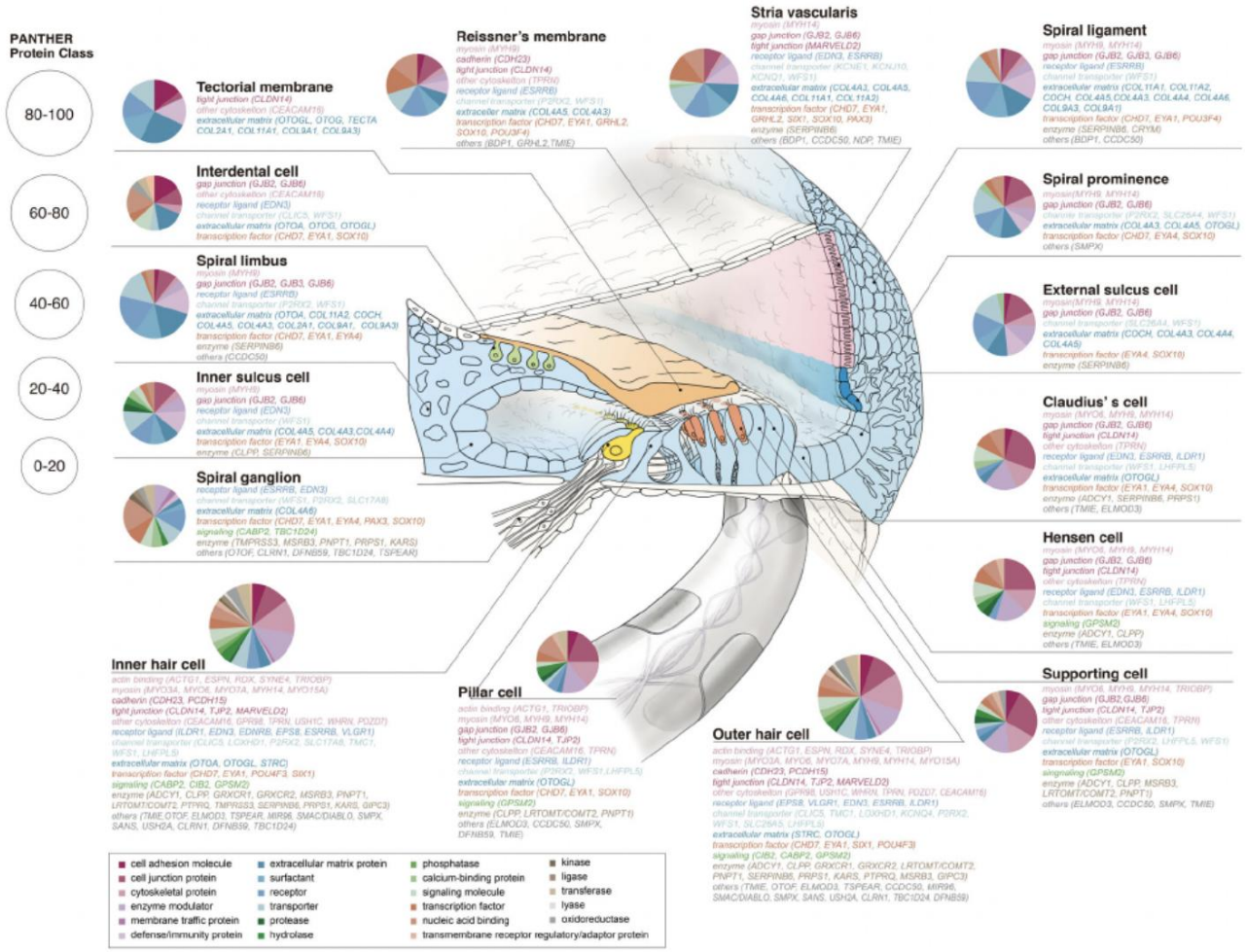


- Currently 1 gene (OTOF)

Scope of the problem

- Congenital / early onset bilateral hearing loss:
  - 1-2/1000 births
  - Genetic causes up to $60 - 80\%$
    - Syndromic (> 400 syndromes with HL) ~30%
    - Non-syndromic ~70%
  - Other causes: congenital CMV (blood spot), rubella, postmeningitis, prematurity, drug toxicity
- Non-syndromic hearing loss extremely heterogenous
  - 80% autosomal recessive (congenital)
  - 20% autosomal dominant (late onset/progressive)
  - X-linked and mitochondrial very rare

Non-syndromic hearing loss



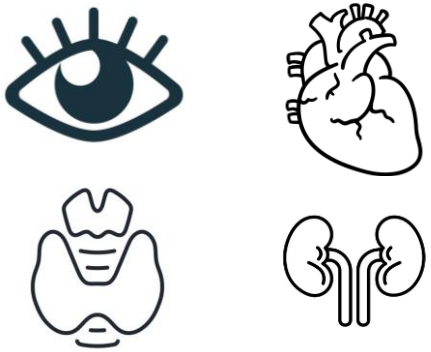
Summary of genes identified to date*
Total nonsyndromic hearing loss associated genes: 156
Autosomal dominant nonsyndromic hearing loss associated genes: 64
Autosomal recessive nonsyndromic hearing loss associated genes: 88
Sex-linked nonsyndromic hearing loss associated genes: 7
Mitochondrial nonsyndromic hearing loss associated genes: 9
Auditory neuropathy associated genes: 5

https://hereditaryhearingloss.org
*19/2/2025

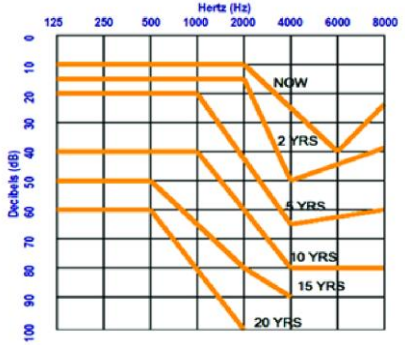
Nishio et al. 2015

Genetic testing isolated bilateral deafness: why?

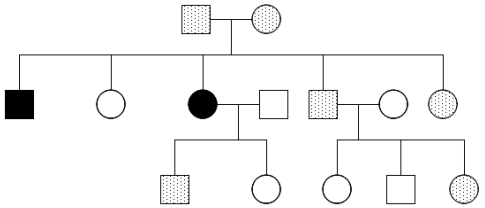
- 95% parents normal hearing
- Question why?



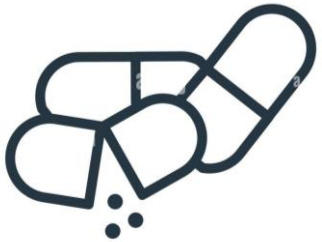
- Associated symptoms?
- Non-syndromic mimics



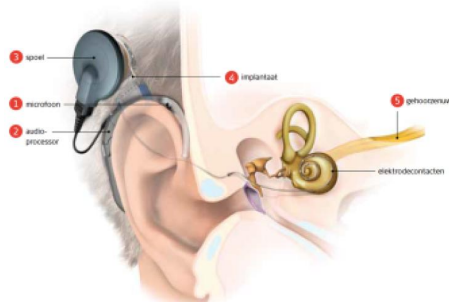
- Prognosis – progression



- Recurrence risk and family planning



- Prevention (eg. aminoglycosides)



- Treatment selection
  - Cochlear implants
  - Gene therapy

Genetic testing isolated bilateral deafness: who?

- Congenital bilateral sensorineural hearing loss (regardless of severity) **YES**
- Early onset bilateral pre/post lingual sensorineural hearing loss **YES**
- Adult onset **YES if young adult, and especially if family history**
- Presbyacousis (age-related late-onset hearing loss) **NO**
- Conductive hearing loss **YES if syndromic presentation**
- Unilateral sensorineural hearing loss **YES if syndromic presentation /consider if inner ear malformations (enlarged vestibular aquaduct cave Pendred)**

Genetic testing isolated bilateral deafness: how?

- Up to 2010: single gene testing mostly *GJB2* ~25% of all autosomal recessive hearing loss cases in Northern Europe. (Parker and Bitner-Glindzics 2015)
- Since 2011: next generation DNA sequencing simultaneous analysis of large number of genes
  - Targeted NGS (gene panels)
  - Exome sequencing (WES-HL gene panel in Antwerp)
    - HPO-based exome wide analysis (esp. testing in small babies, risk of missing syndromes)
    - Informed consent
    - Clinical information, audiograms
    - Singles/**trios** (eg. compound heterozygotes)
    - Variant classification in multidisciplinary setting

Challenges in genetic counseling hearing loss clinic

- **Diagnosis of condition with later onset symptoms in infants (Usher syndrome)**
- **Genes with syndromic and non-syndromic presentation (also Usher syndrome)**
- **Genes with both AD and AR inheritance**

Classification of genes

- **DFN (deafness)**
- **DFNA:** autosomal dominant
- **DFNB:** autosomal recessive
- **DFNX or DFNY:** x-linked or y-linked
- **MT:** mitochondrial
- **AUN:** auditory neuropathy spectrum disorder
- **DFNM:** modifier genes

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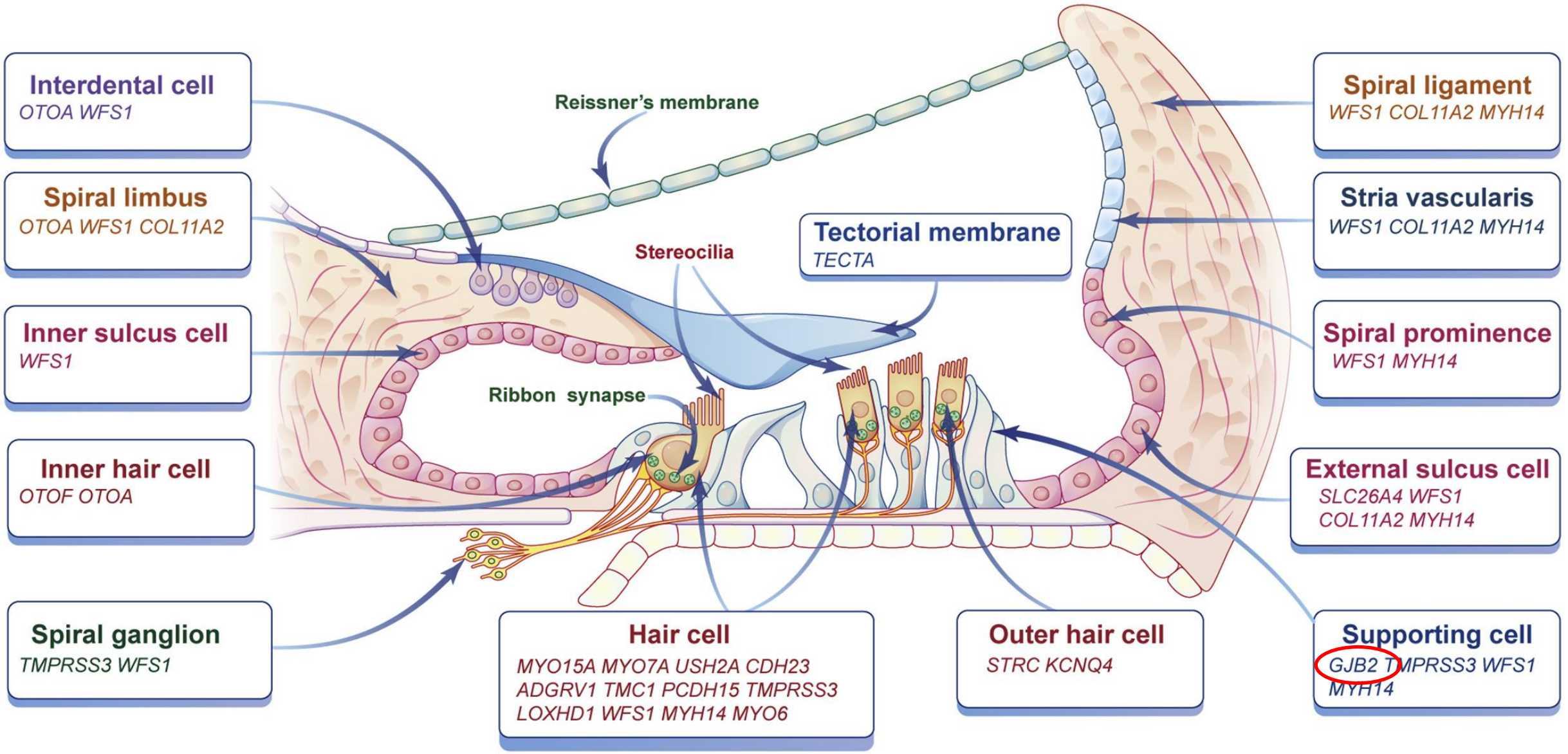
- Syndromic hearing loss

GJB2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WFS1 MYH14
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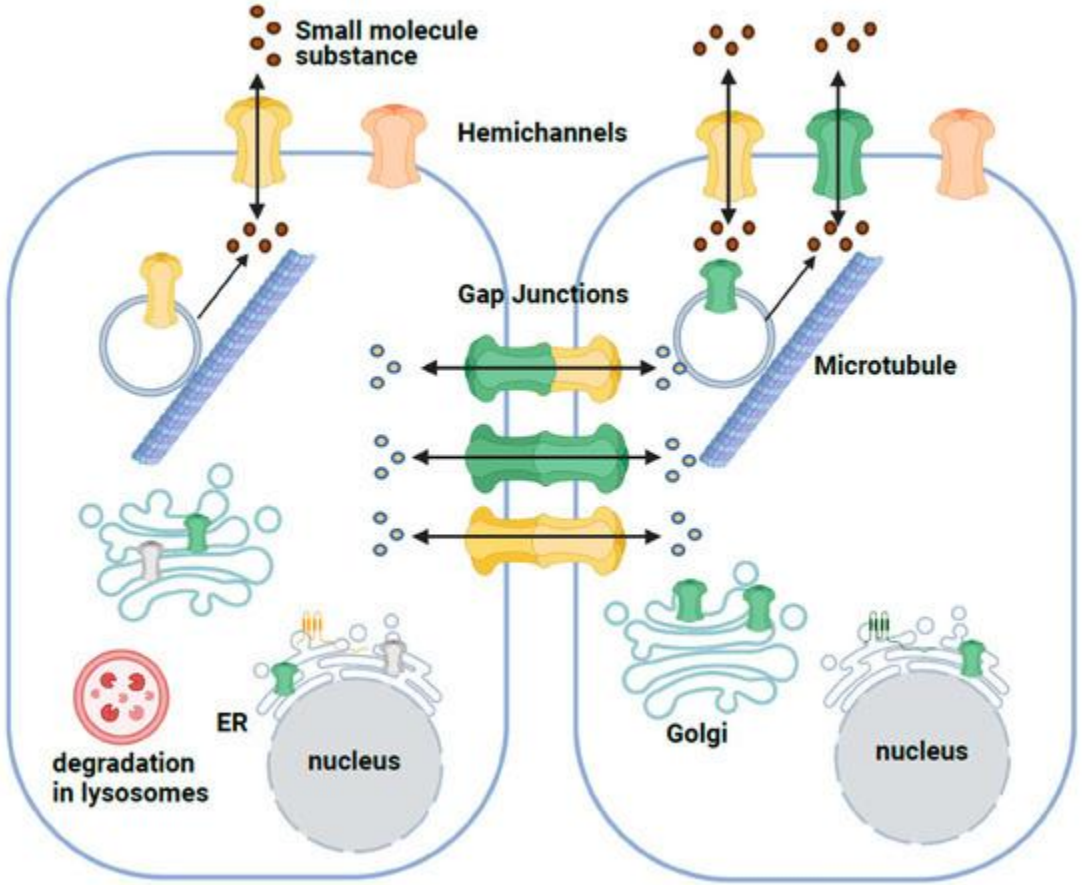
SLC26A4 WFS1
COL11A2 MYH14
Supporting cell
GJB2 TMPRSS3 WFS1
MYH14

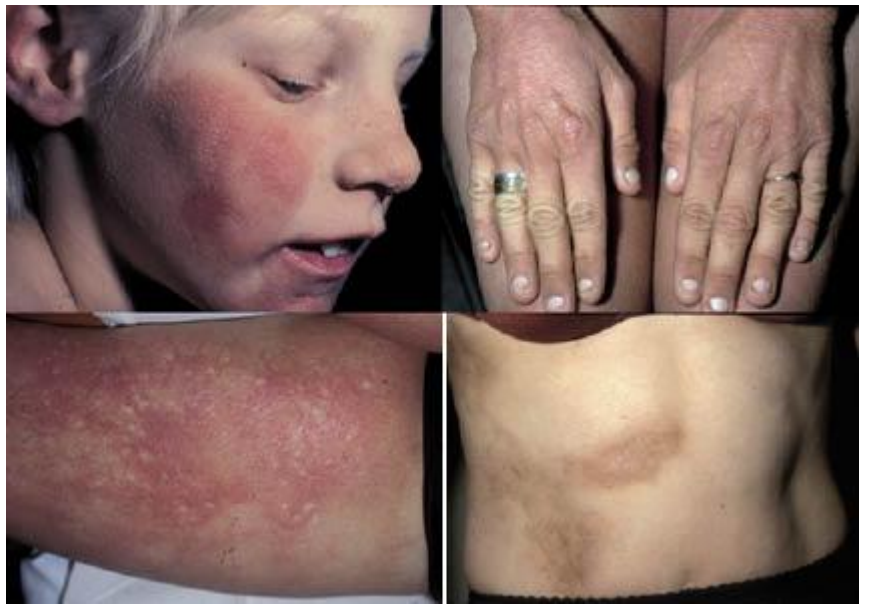
GJB2-associated hearing loss

- DFNB1 locus:
  - *GJB2* – Connexin 26
  - *GJB6* – Connexin 30
- Gap junctions → K^+ homeostasis in cochlea
- AR hearing loss / digenic
- Loss-of-function
- Typical:
  - Congenital
  - Mild-profound
  - Non-progressive (70%)
- Genotype-phenotype correlation ~ residual function:
  - Biallelic truncuating most severe
  - But also variation within families
- ~3% of population are carriers
- Treatment with CI good results

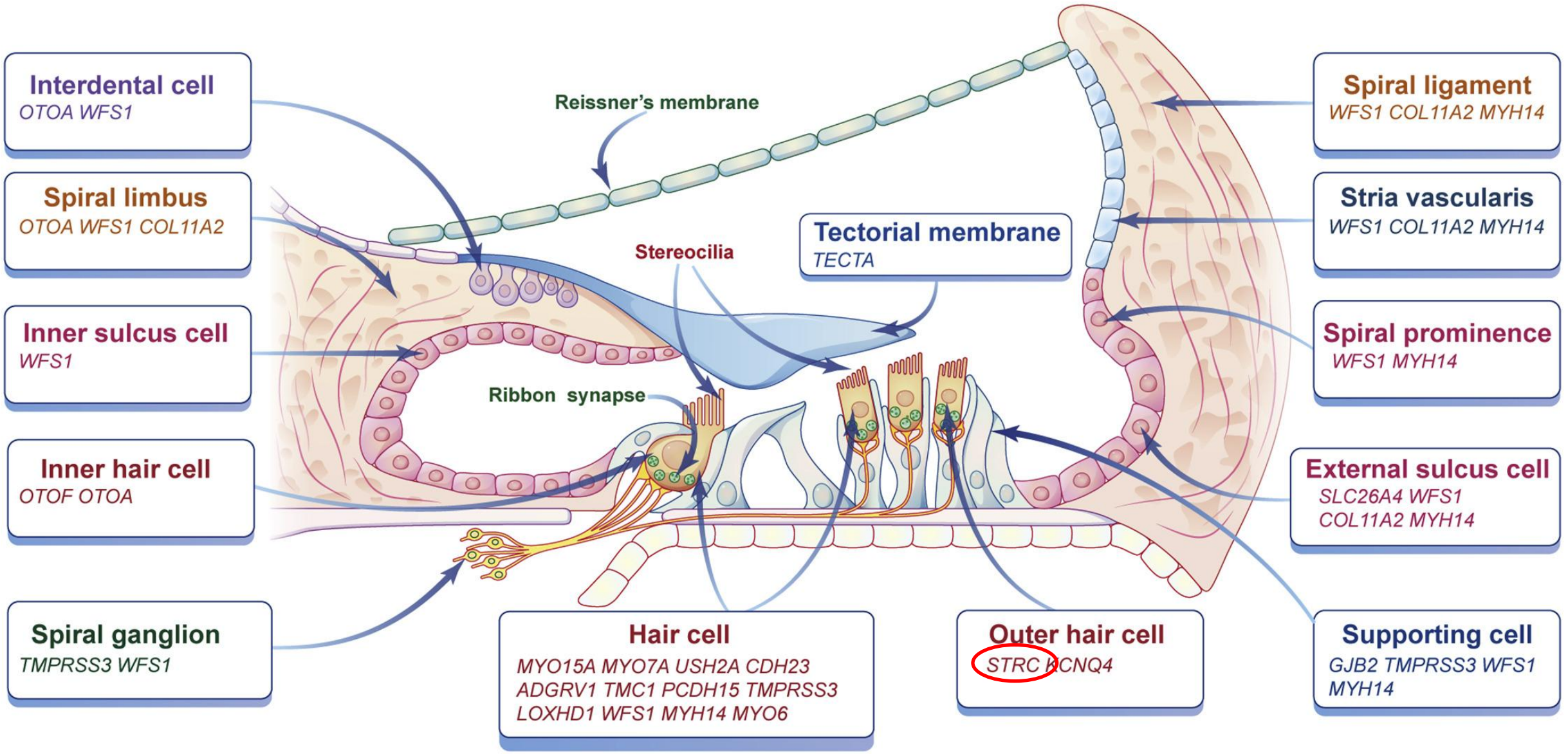


GJB2-associated hearing loss

- Recently also later onset and progressive forms published (especially for non-truncuating variants)
- *GJB2* dominant form with skin findings e.g. ichtyosis/keratoderma (syndromic)/isolated hearing loss (rare)



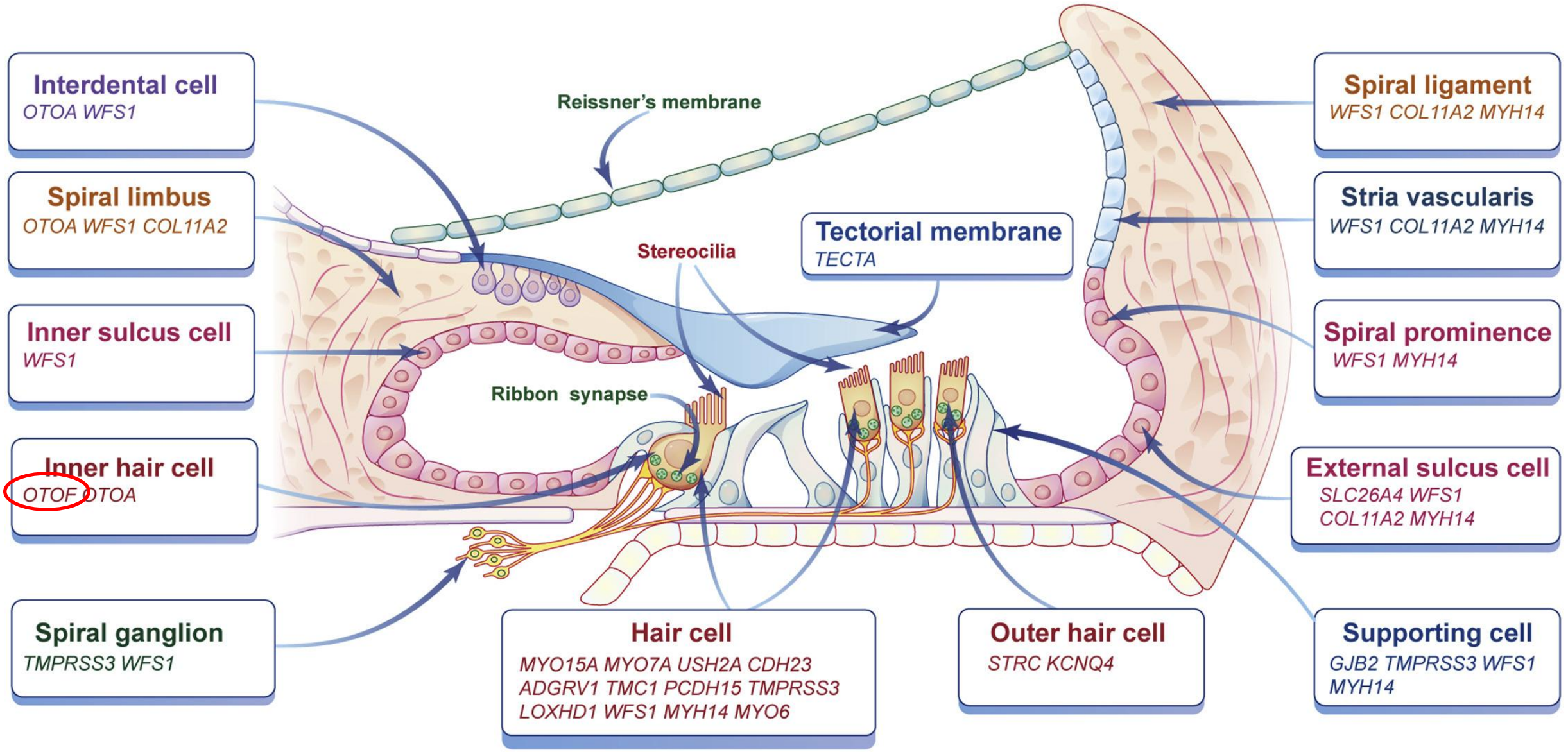
Stereocillin



Stereocilin

- Sensory hair cells in inner ear (sound wave mechanoreception)
- AR hearing loss
- 2nd most common cause of hereditary SNHL
- ~30% of mild-moderately severe SNHL
- May pass newborn hearing screening
- Sequencing challanges:
  - CNVs
  - Pseudogene
- Contiguous deletion of *STRC and CATSPER2* are associated with increased risk for intertility in males (abnl sperm mobility) – Deafness Infertility syndrome

OTOF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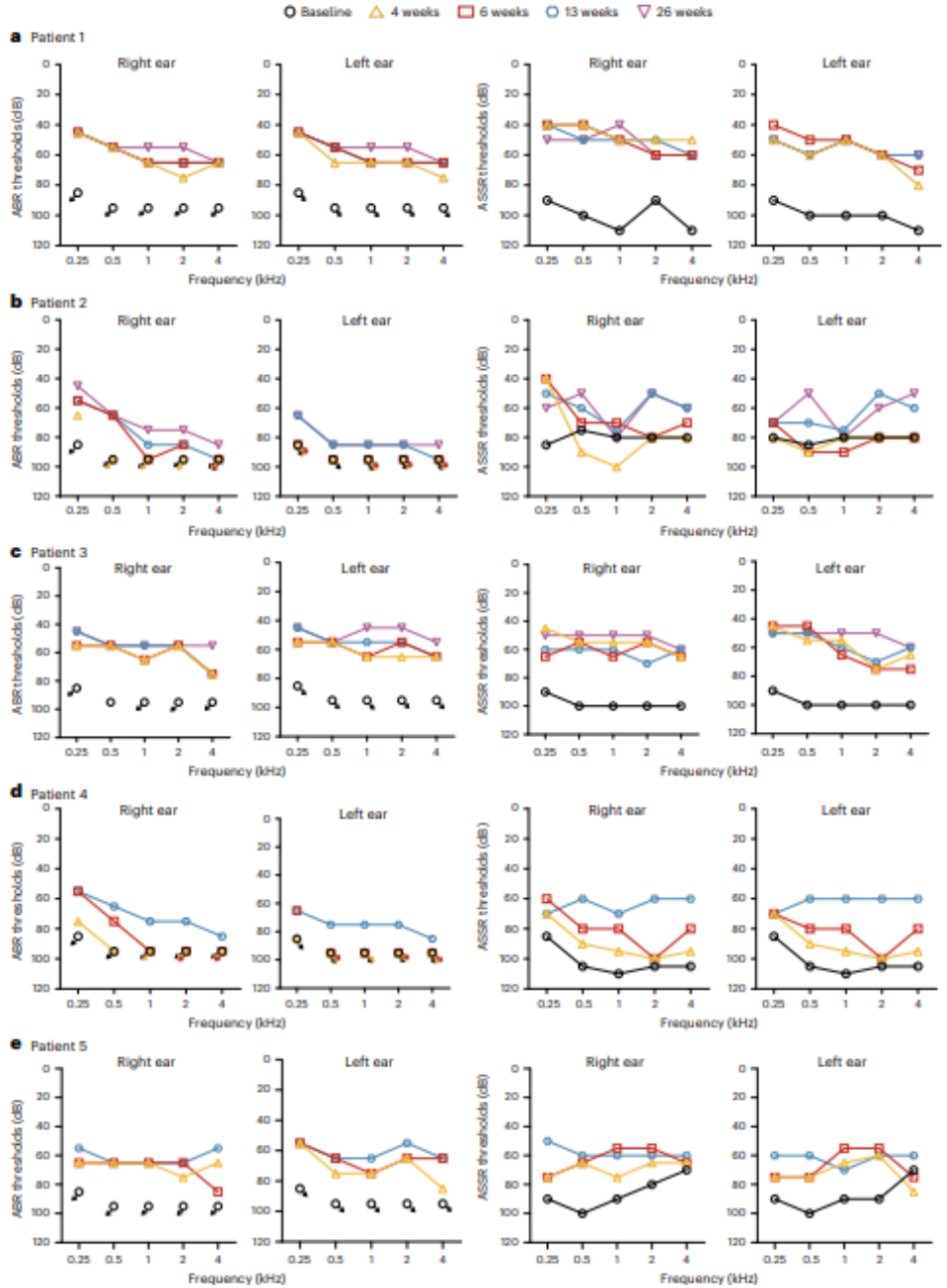
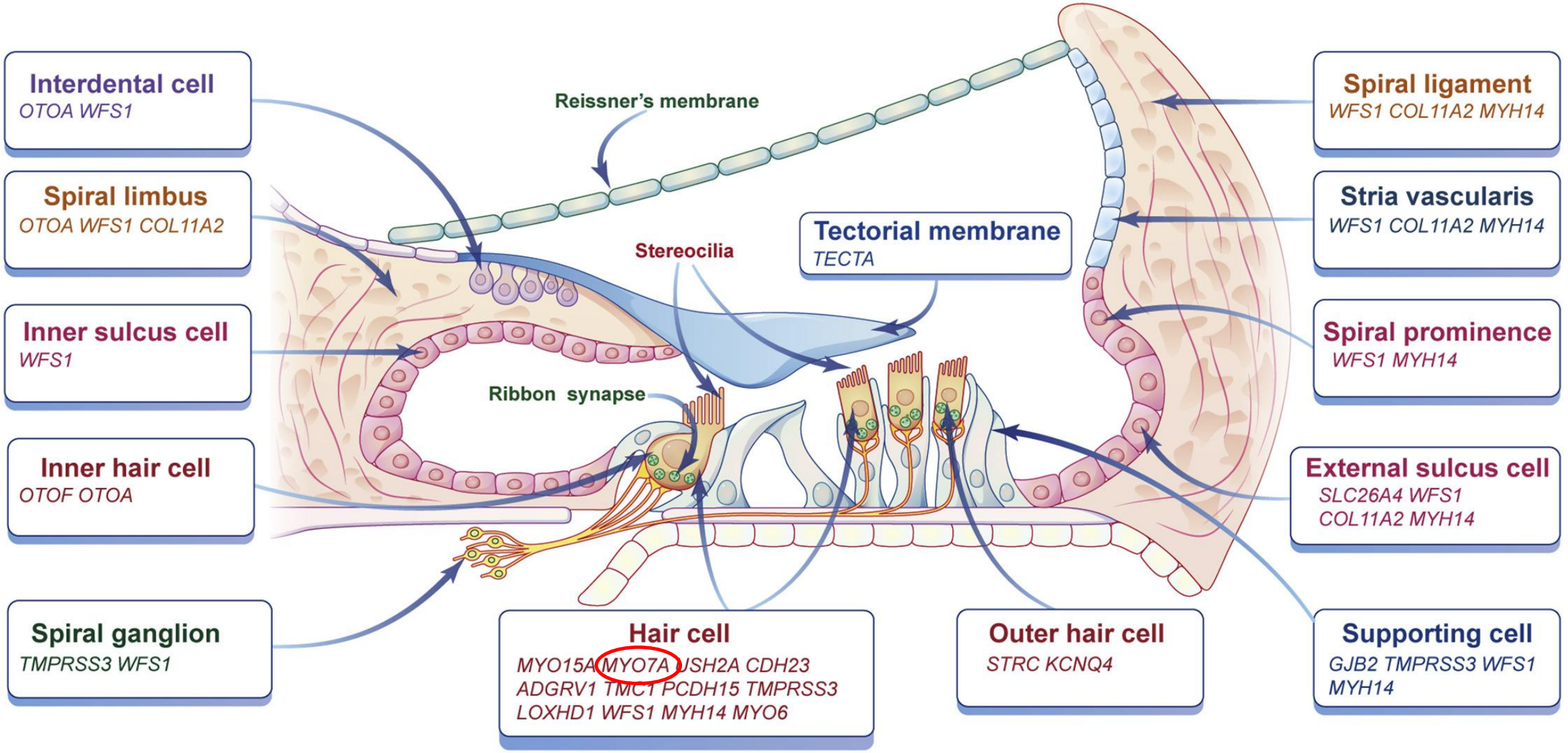
OTOF

- Otoferlin
- Defect synaptic transmission cochlear inner hair cells --> auditory nerve = auditory neuropathy
- AR
- OTAE normal / Algo&BERA abnormal
- Typical: congenital/prelingual, severe-profound
- Atypical: normal/moderate --> severe if fever
- Can be progressive
- Gene therapy: AAV with OTOF transgene


Baseline
4 weeks
6 weeks
13 weeks
26 weeks
a Patient 1
b Patient 2
c Patient 3
d Patient 4
e Patient 5
Right ear
Left ear
ABR thresholds (dB)
ASSR thresholds (dB)
Frequency (kHz)
0.25
0.5
1
2
4
0
20
40
60
80
100
120

MYO7A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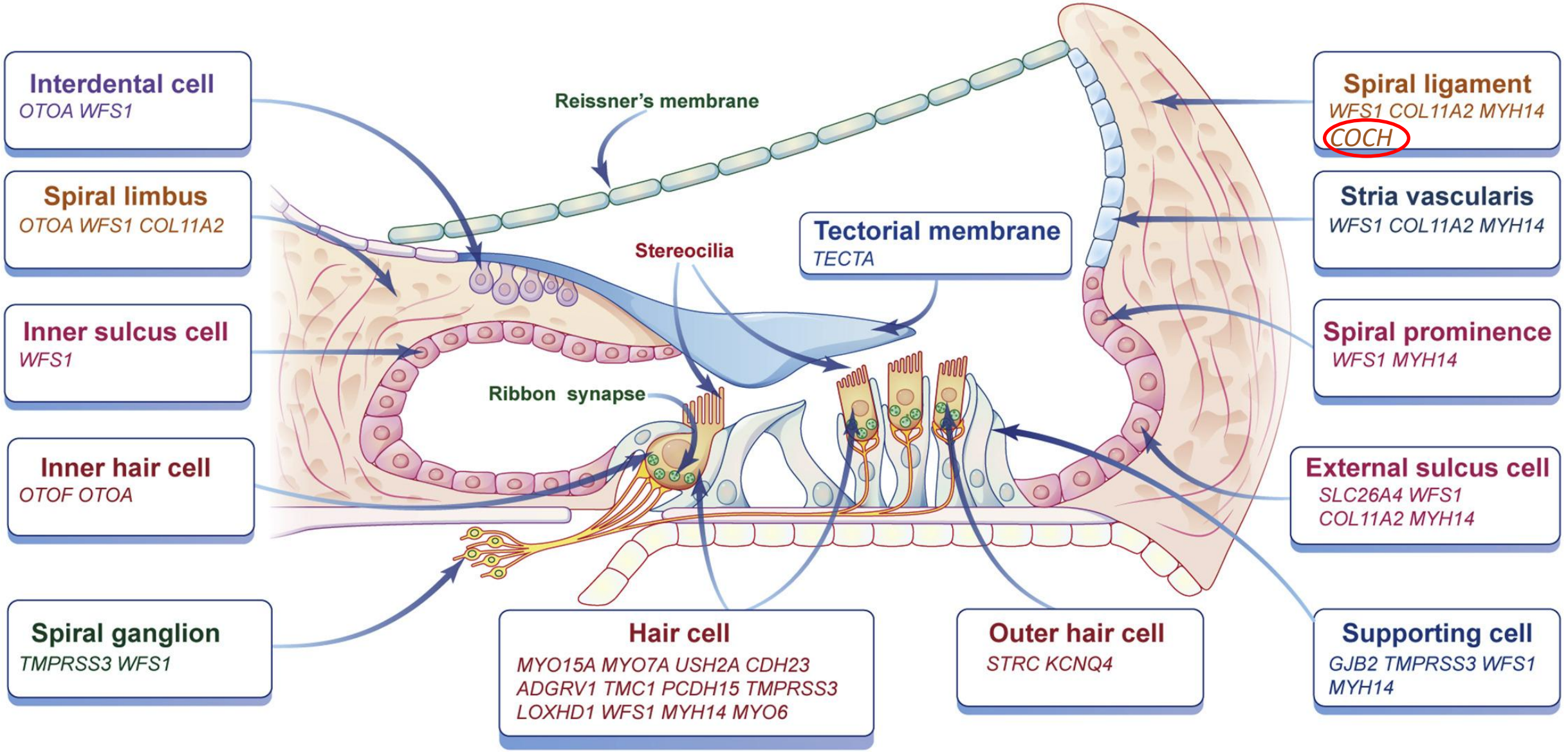
MYH14

MYO7A

- Myosin VIIA
- One of several myosins involved in normal functioning of stereocillia
- Also expressed in retina
- Different clinical phenotypes:
  - AR nonsyndromic hearing loss (DFNB2)
  - AD nonsyndromic hearing loss (DFNA11)
  - Usher syndrome type 1B
  - Isolated retinopathy (specific variants)
- Genotype-phenotype correlation:
  - Inframe/missense: more AD HL (dominant negative effect?)
  - Biallelic null variants: more Usher syndrome (full LoF?)
  - Null + missense variants: more AR nonsyndromic HL (partial LoF?)
  - Check vestibular function! Abnormal in Usher IB
- Multiple inheritance patters / different (syndromic vs non-syndromic) presentations also applicable to other HL genes

COCH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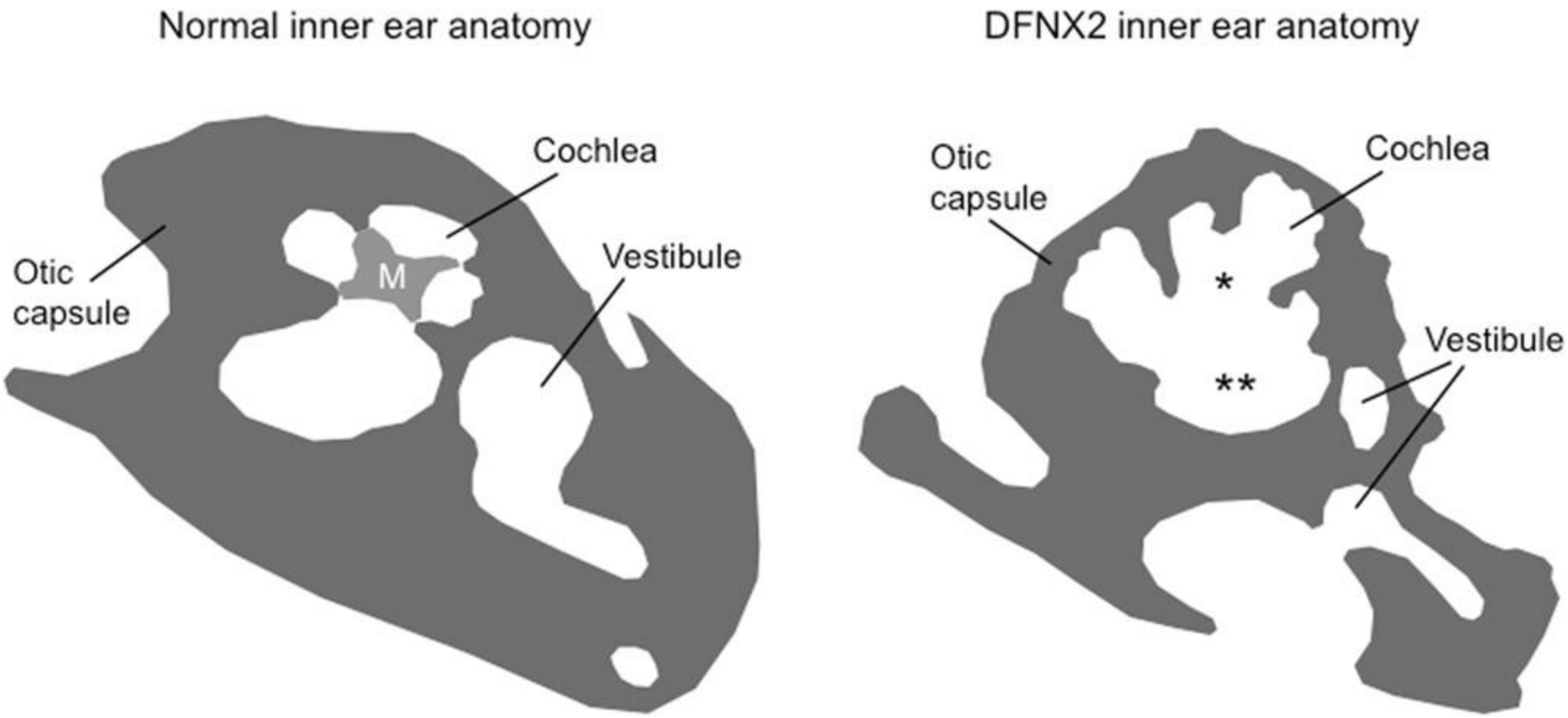
COCH

- Cochlin
- Important component extracellular membrane
- Dominant negative effect: accumulation of mutant protein
- AD (DFNA9)
- Pogressive cochleo-vestibular dysfunction
- c.151C>T Belgian/Dutch founder mutation --> complete penetrance, onset in young adulthood
- Downward sloping audiogram
- Associated vestibular symptoms (vertigo), tinnitus

POU3F4



Abnormal mesenchymal cell differentiation in periotic bone

POU3F4

- POU domain, class 3, transcription factor 4
- LoF
- X-linked
- Inner ear malformation, fixation at the stapes
- Non-syndromic
- Conduction type, mixed or sensorineural hearing loss, typically profound in males with milder hearing loss in females
- Poorer outcomes CI

Mitochondrial

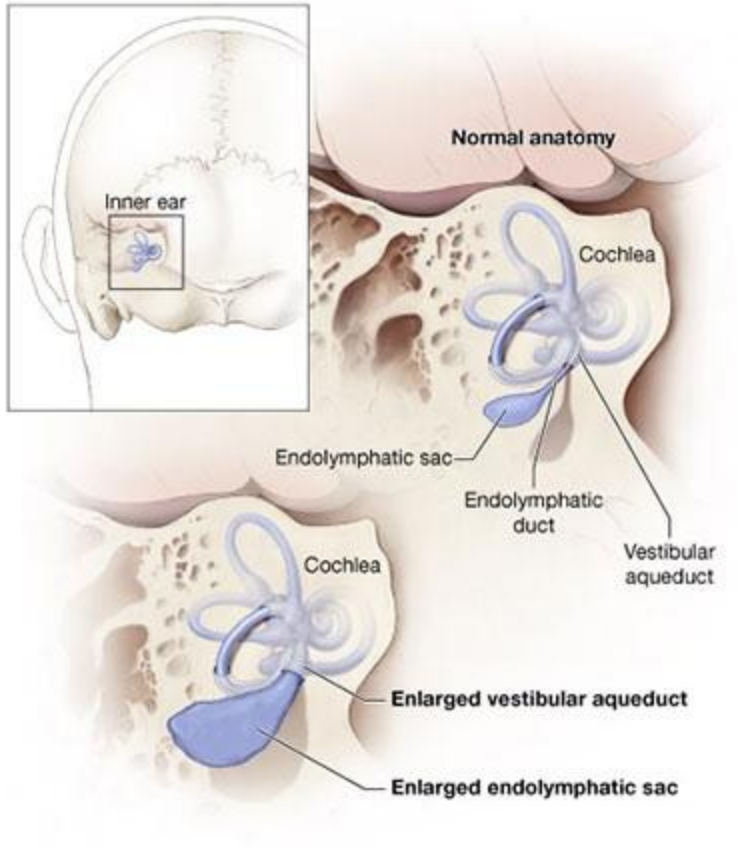
- Moderate-to-profound hearing loss, often high frequencies
- Matrineal inheritance
- MT-RNR1 (12S ribosomal RNA) 70%
- MT-TS1 (transfer RNA Ser(UCN)) 30% (syndromic: palmoplantar keratoderma)
- MT-RNR1: aminoglycoside ototoxicity
  - Bilateral, severe to profound
  - Days to weeks after first dose (any amount)
- Homoplasmy and heteroplasmy (depends on mutation and ~ with penetrance)
- Syndromic forms:
  - Associations with diabetes (high frequency HL)

Non-syndromic mimics

- **Initially present as isolated hearing loss**
- **Other sympoms become apparent years later**
- **Genes for**
  - Pendred syndrome
  - Usher syndrome
  - Deafness/Infertility syndrome (see STRC)

Pendred syndrome

- *SLC26A4* gene solute carrier family 26 member 4
- Anion transporter (pendrin)
- Defect --> acidification of endolymphatic fluid
- Antenatal formation of enlarged vestibular aqueduct
- Detectable on MRI
- AR
- Variable onset fluctuating/progressive HL
- Vestibular dysfunction
- Thyroid: goiter between 10-20 years in some (10%) patients, FU until adulthood (blood and echo)
- Monoallelic pathogenic variant SLC26A4 with bilateral EVAS is also at risk (second variant (still) unknown)
- CEVA haplotype



Usher subtypes

Usher subtype	Hearing loss	Retinitis Pigmentosa	Vestibular dysfunction
USH1	Profound congenital	Prepubertal onset	Severe (bilateral vestibular areflexia)
USH2	Mild to severe Congenital	Postpubertal onset	Absent
USH3	Mild and progressive	Postpubertal onset or variable	Variable

Hearing loss in Usher syndrome

USH1

- Bilateral congenital severe hearing loss
- Detection at neonatal Algo screening
- 11-12 % of *GJB2* - in pediatric CI population (Kimberling et al. 2010)
- Normal inner ear scans
- AR: MYO7A (1/165 carrier), USH1C, CDH23, PCDH15, USH1G and CIB2

Hearing loss in Usher syndrome

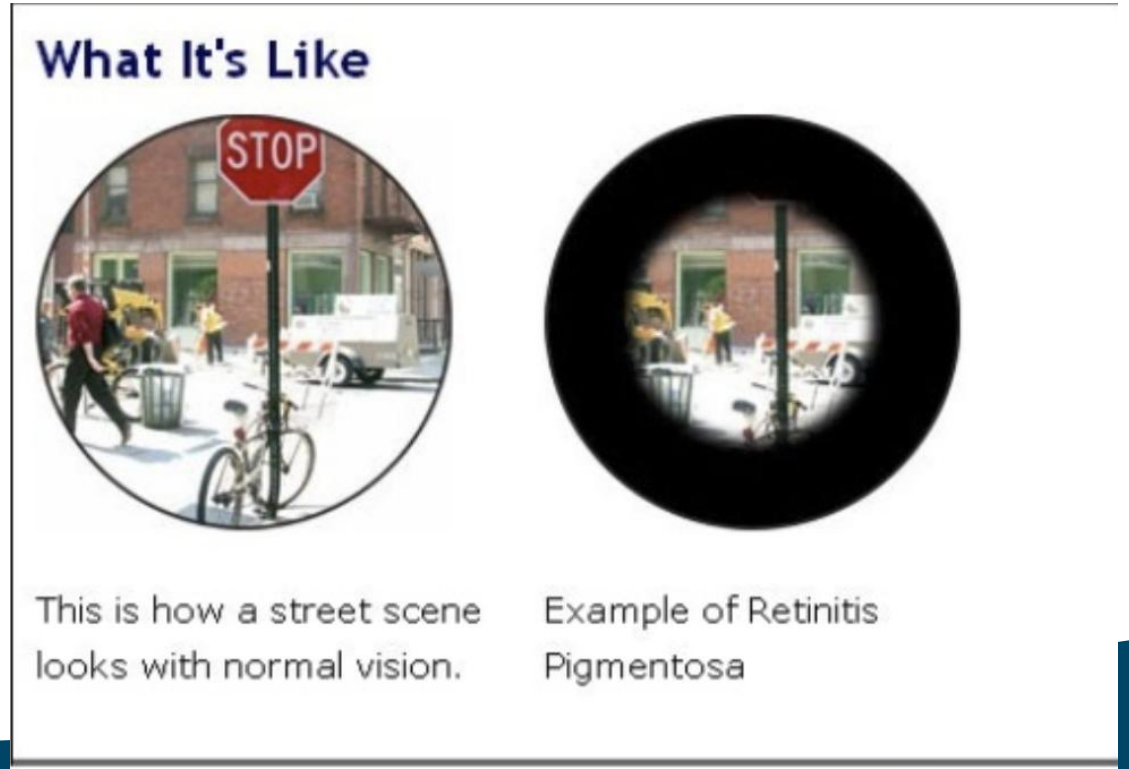
USH2

- Congenital, high tone, medium-severe
- Sometimes (unexpectedly quickly) progressive
- Detection at neonatal Algo screening
- AR: ADGRV1, USH2A, or WHRN

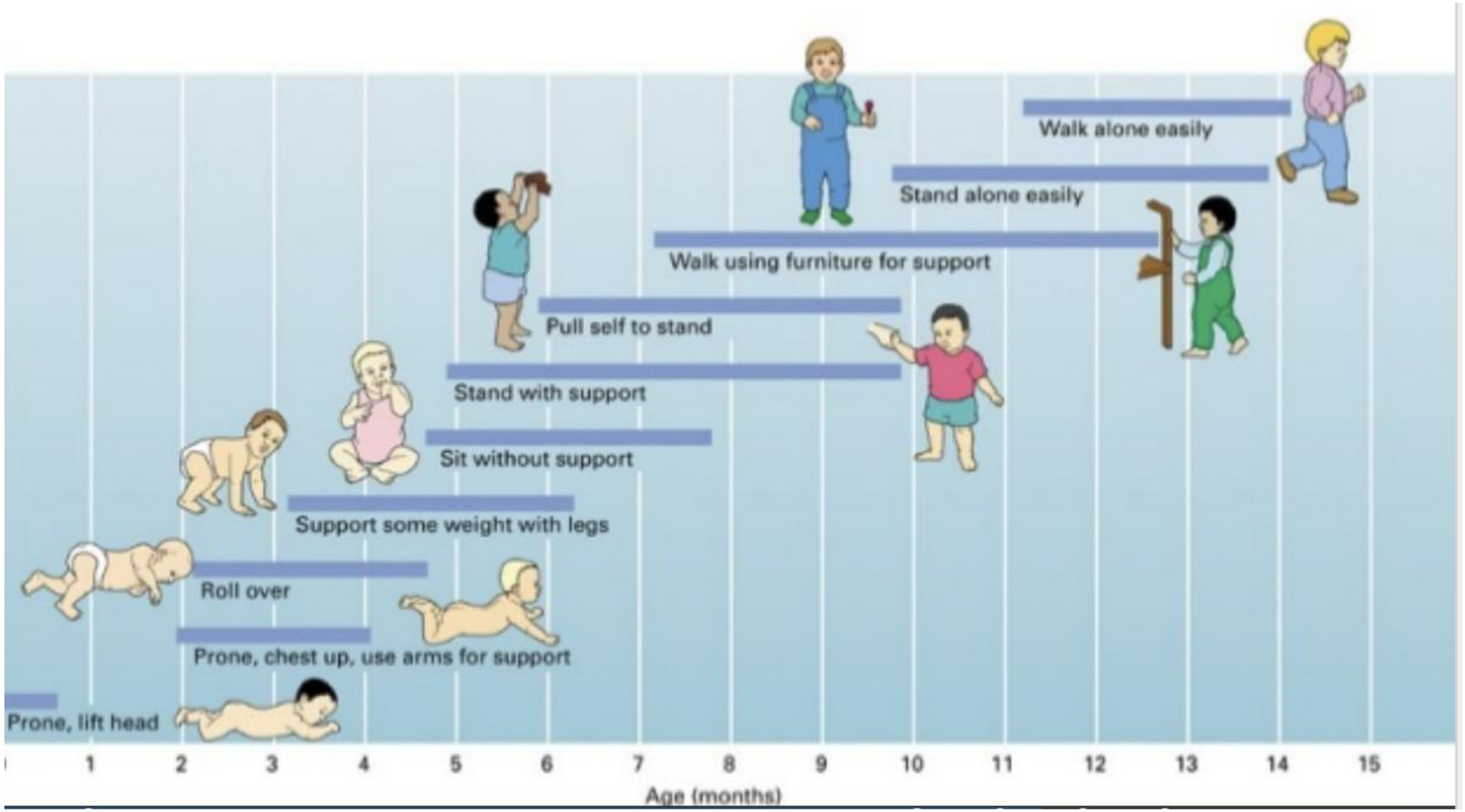
USH3

- Progressive hearing loss
- Postlingual– detection ~10 years
- Somstimes presentation with visual symptoms
- Variabiliy in severity and progression rate (0-4dB/y)
- AR: CLRN1, HARS1

Retinitis pigmentose symptoms in US



Vestibulair disfunction in USH1



Late onset of independent walking (> 18 months) and delay in motor milestones

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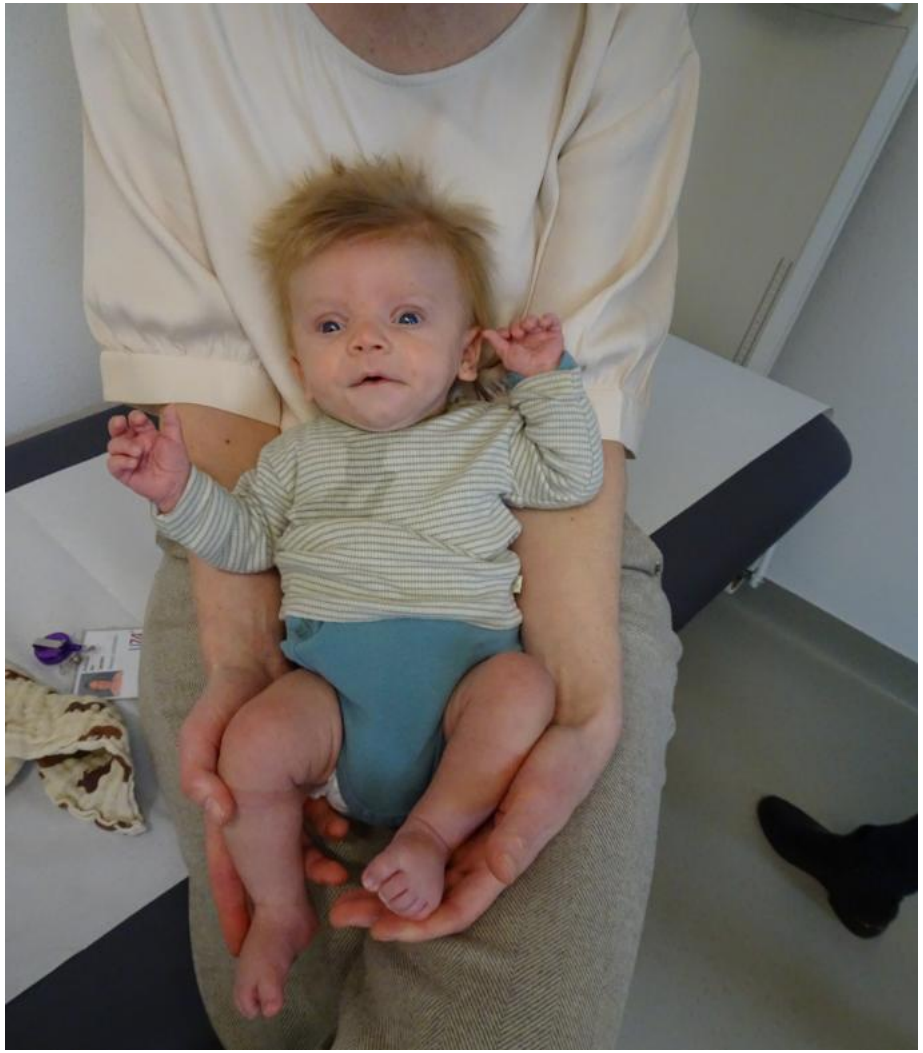
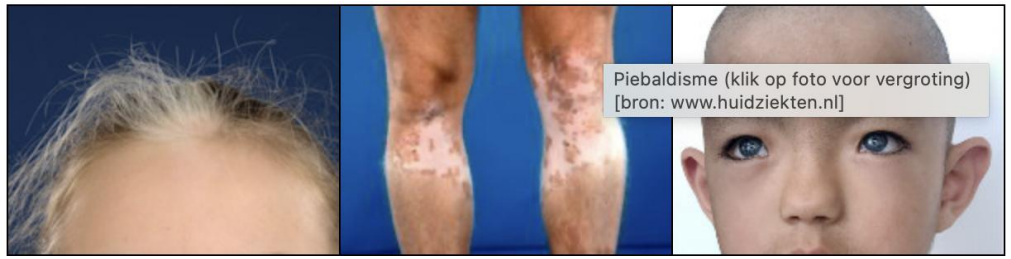
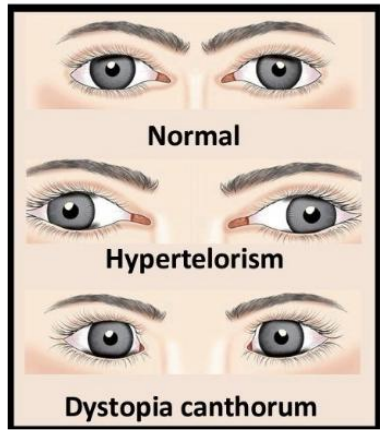
- **Syndromic hearing loss**





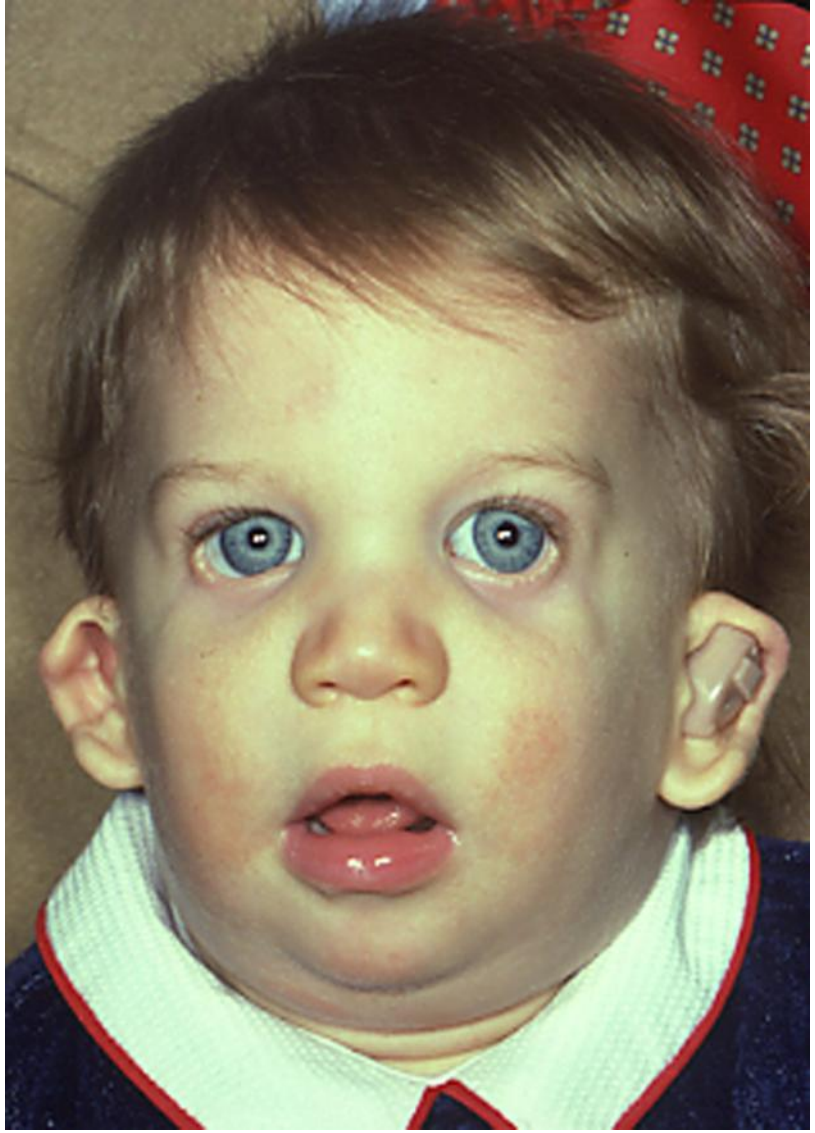


Hirshprung disease
Light hair, blue eyes
Broad nasal root
Bilateral Algo refer

Heterochromia iridi
Pigmentation defects, white hairlock
Dystopia canthorum

Waardenburg

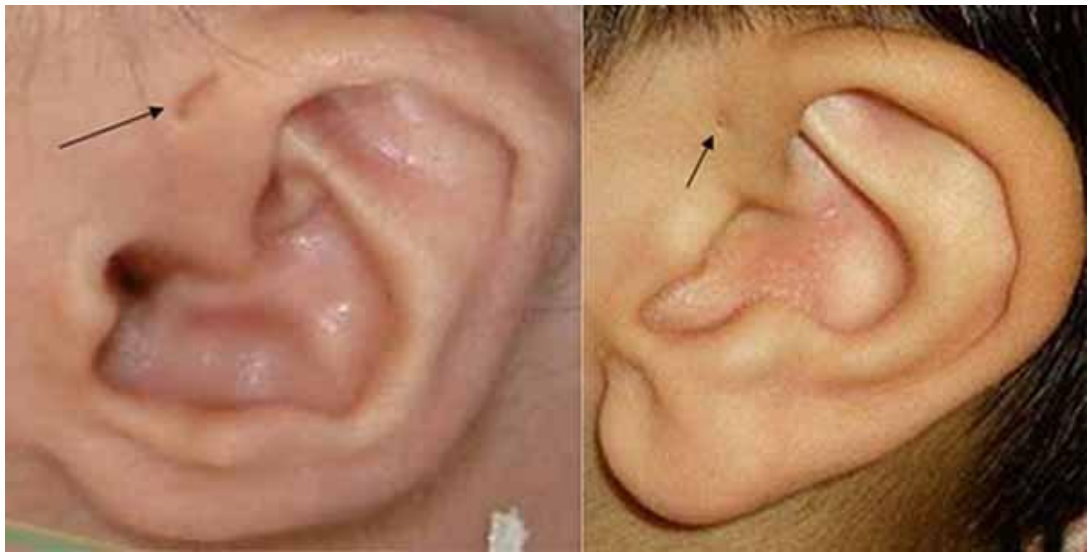
- **Clinical variability**
- **AD**
- **Typical features: white forelock, broad nasal root, heterochromia of the iris**
- **Type 1:**
  - Dystopia cantorum (telecantus), broad nasal root, short philtrum, retroposition of the maxilla
  - PAX3
- **Type 2:**
  - Normal inner canthi, hearing loss, heterochromy
  - MITF, WS2B, WS2C, SOX10, KITLG
- **Type 3:**
  - Type 1+ skeletal abnormalities, ID, microcephaly
  - PAX3
- **Type 4:**
  - Type 2 + Hirsprung. Pigmentation abnormalities of the skin, eyes and hair.
  - EDNRB, EDN3, SOX10

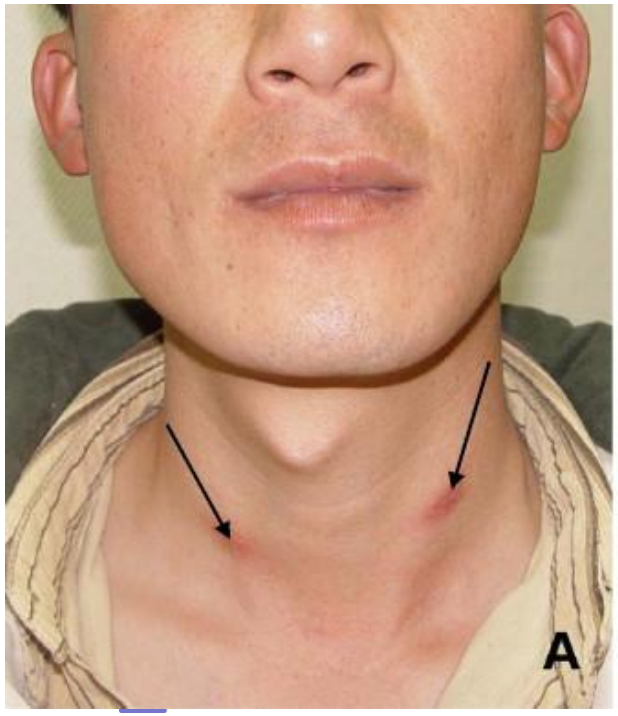


Midface hypoplasia
Dysplastic ears
Cleft palate
Conductive hearing loss

Treacher Collins

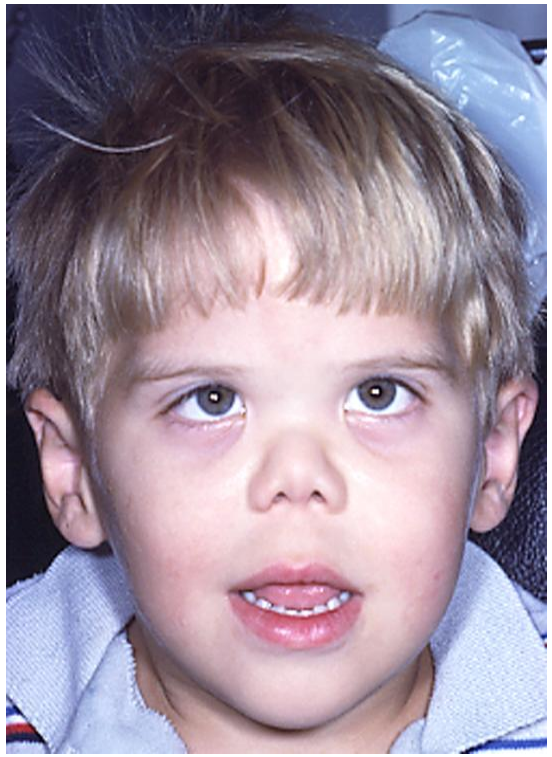
- Lower eyelid abnormalities (coloboma), malar hypoplasia, downslanted palpebral fissures, and micro- or retrognathia
- AD
  - *TCOF1, POLR1D, POLR1B*
- AR (rare)
  - *POLR1C, POLR1D*

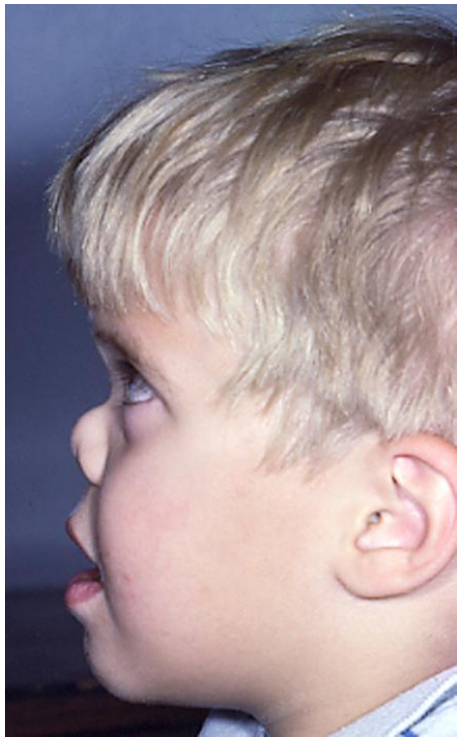




Branchio-oto-renal spectrum disorder

- Deafness: mild to profound; conductive, sensorineural, or mixed
- Preauricular pits/tags, dysmorphic ears
- External auditory canal & inner ear abnormalities
- Variable congenital renal abnormalities (not fully penetrant)
- AD
  - *EYA1, SIX1, SIX5*





Myopia
Cleft palate

Stickler syndrome

- Ocular findings (myopia/retinal detachment)
- Hearing loss (high frequency)
- Midfacial underdevelopment and cleft palate
- Mild spondyloepiphyseal dysplasia and/or precocious arthritis
- AD/AR
  - COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3

Stickler syndrome

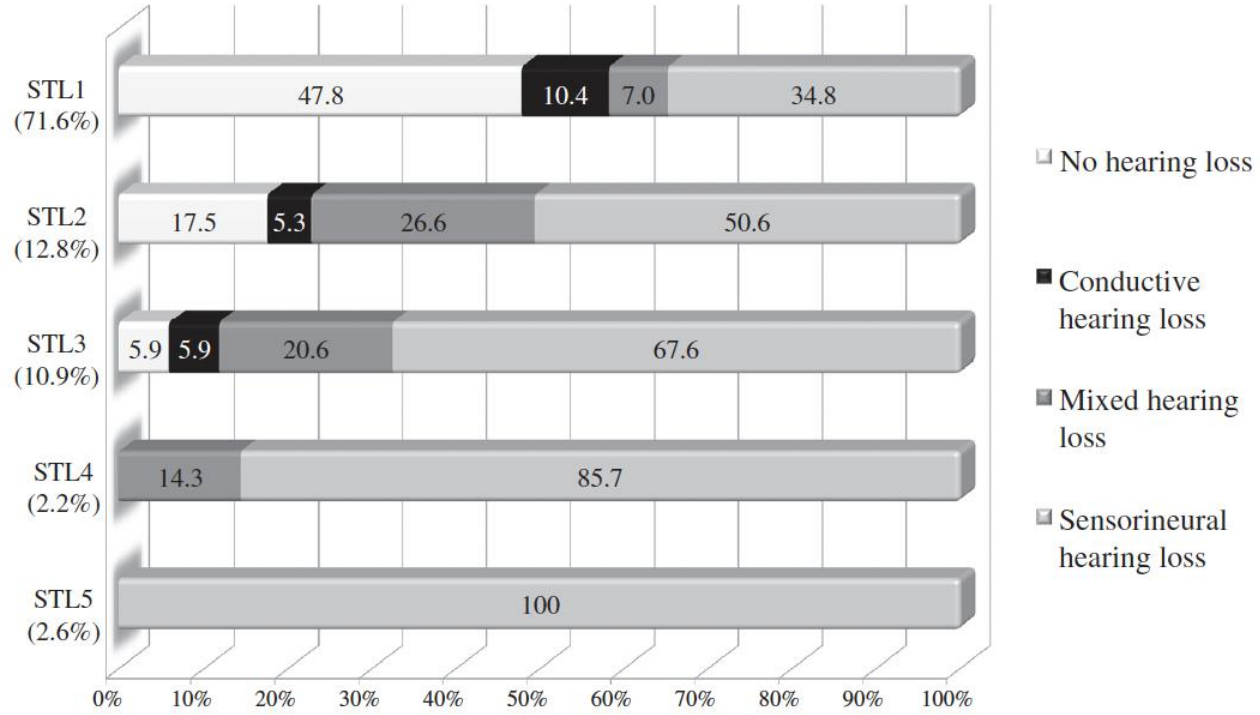
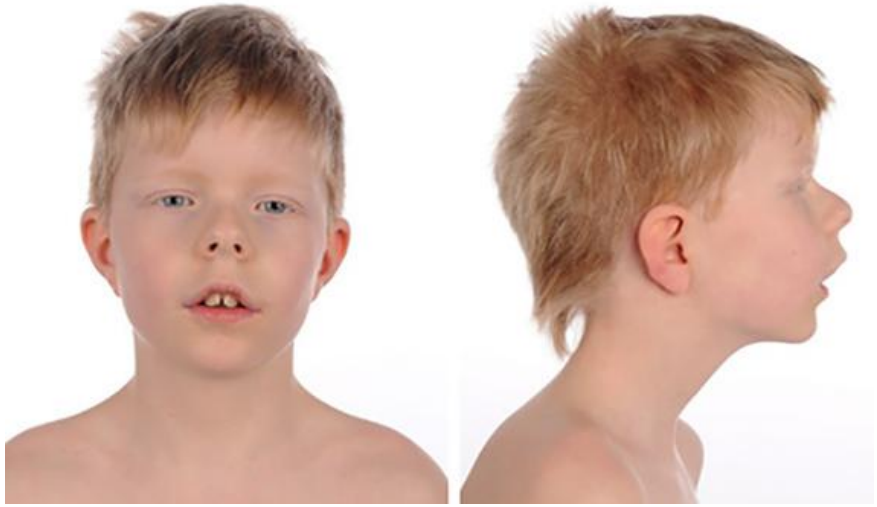


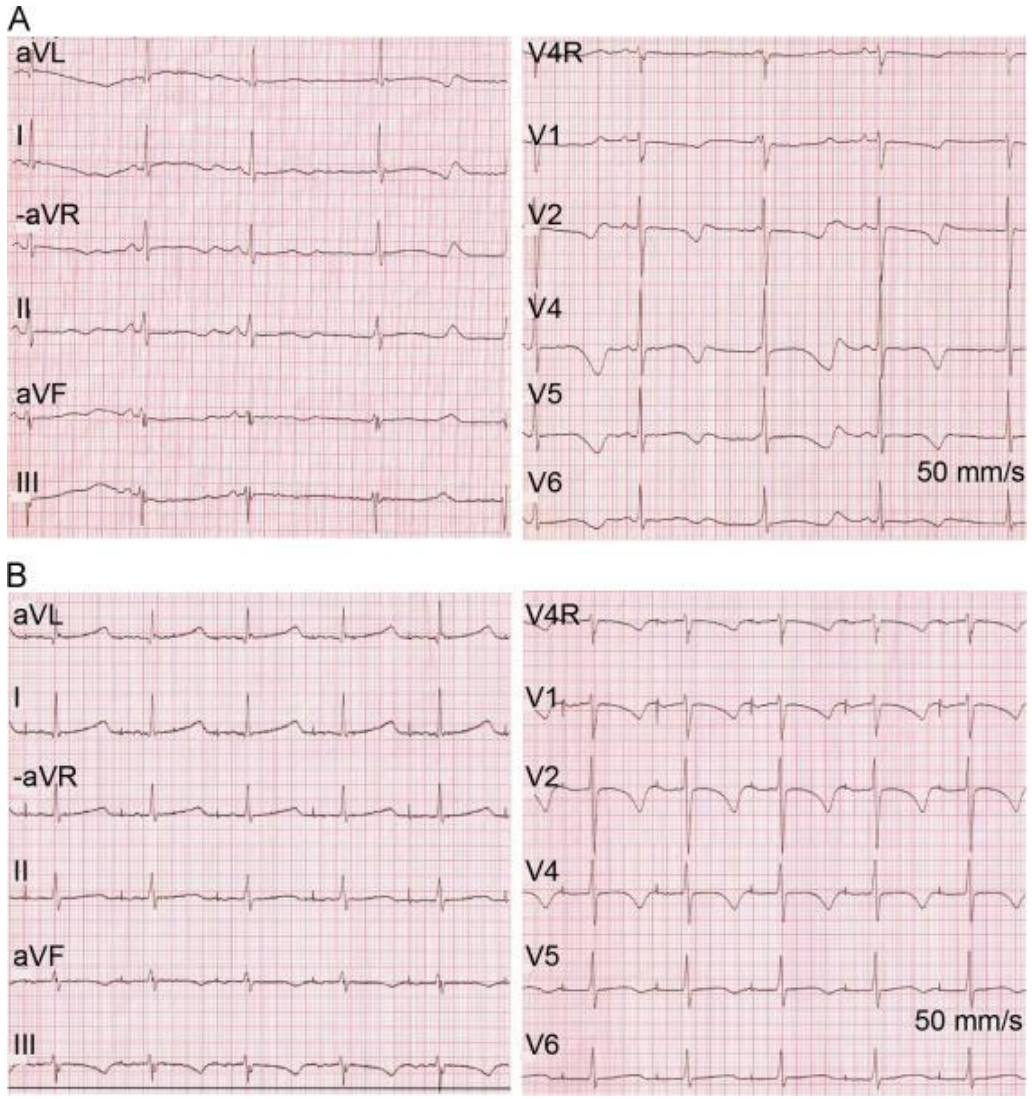
Figure 4 Hearing phenotype in distinct Stickler types. The percentages of hearing loss and its type for each type of Stickler syndrome (according to the affected gene) are shown in this figure. The group of hearing-impaired patients in which the type was not mentioned (6.4%), was proportionally divided among the three hearing loss groups.



Short stature
Mild developmental delay
Anteverted nares, prominent incisors, thin upper lip vermillion

KBG syndrome

- Clincal features
  - Macrodontia, triangular face, brachycephaly, synophrys, hypertelorism, broad eyebrows, prominent ears, prominent nasal bridge, bulbous nose, anteverted nares, long philtrum, and thin vermilion of the upper lip
  - Short stature, developmental delay / intellectual disability, and behavioral issues.
  - Feeding difficulties
  - Skeletal anomalies (brachydactyly, large anterior fontanelle with delayed closure, scoliosis)
  - Hearing loss (conductive, mixed, and sensorineural)
  - Epilepsy
  - Brain malformations
- AD
  - ANKRD11



Recurrent sudden syncopes
Familial syncopes/sudden death

Jervell-Lange-Nielsen

- Long QT syndrome x hearing loss
- Lethal by 15 years in 50% if untreated
- AR
  - KCNQ1, KCNE1

Some other syndromic diagnoses to consider

- **Renal dysfunction, hematuria, proteinuria, eye lens defect or retinopathy in males:** Alport
- **Fractures:** Osteogenesis Imperfecta
- **Craniosynostosis, developmental delay, strabismus:** Muenke

Conclusion

- **Hearing loss:**
  - Clinically and genetically diverse
  - Often treatable!
  - Merits genetic testing with a broad scope
  - Beware of early presentations/non-syndromic mimics