Sensorion KOL Event – GJB2 gene related hearing loss

DISCLAIMER

As a reminder, during today‘s call, we will make forward looking statements based on our current expectations. Our actual results may differ materially from such statement.

Q&A

Today there will also be an opportunity to ask questions. Please wait until the end.

PRESENTATION & REPLAY

The presentation will be available on Sensorion‘s website and a replay will be available later today

Today’s agenda

Introduction
Nawal Ouzren, Chief Executive Officer of Sensorion

Clinical aspects, current treatments landscape and unmet medical needs in treating patients with a pediatric onset of GJB2-related hearing loss as well as the role of the GJB2 gene
Thomas Lenarz, M.D., Ph.D., Pofessor of Otorhinolarygology and Chair of the Department of Otorhinolaryngology, Medical University of Hannover, Germany

Sensorion: Gene Therapy Capabilities
Geraldine Honnet, Chief Medical Officer of Sensorion





GJB2 Gene Related Hearing Loss

Thomas Lenarz

Dept Otolaryngology, Hannover Medical School

Chair: Thomas Lenarz, MD PhD

Sensorion KOL Webinar, May 10, 2021

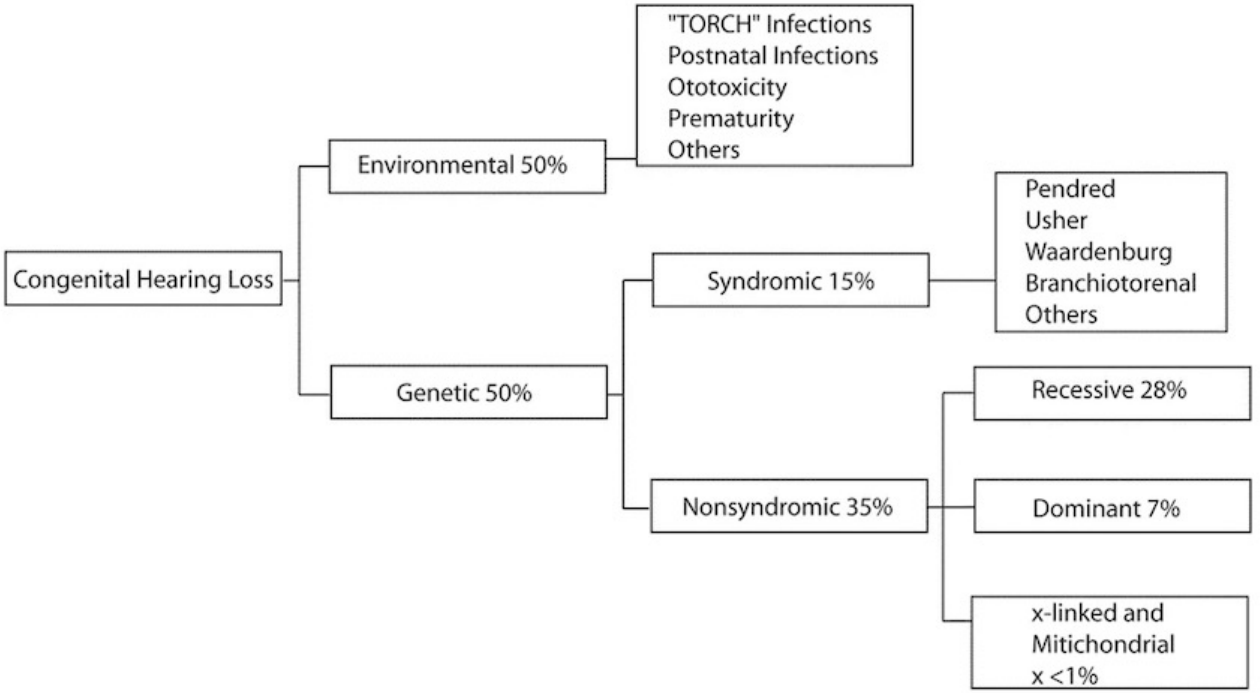
Clinical relevance of hearing loss

15 % of the population affected, growing with age
Children: 2 / 1000 affected

Etiology of Hearing Loss

- Genetics: Children 50 – 70 %, adults 30 %
- Noise
- Aging
- Ototoxic agents
- Infections
- Trauma
- Unknown

Genetics in Hearing loss

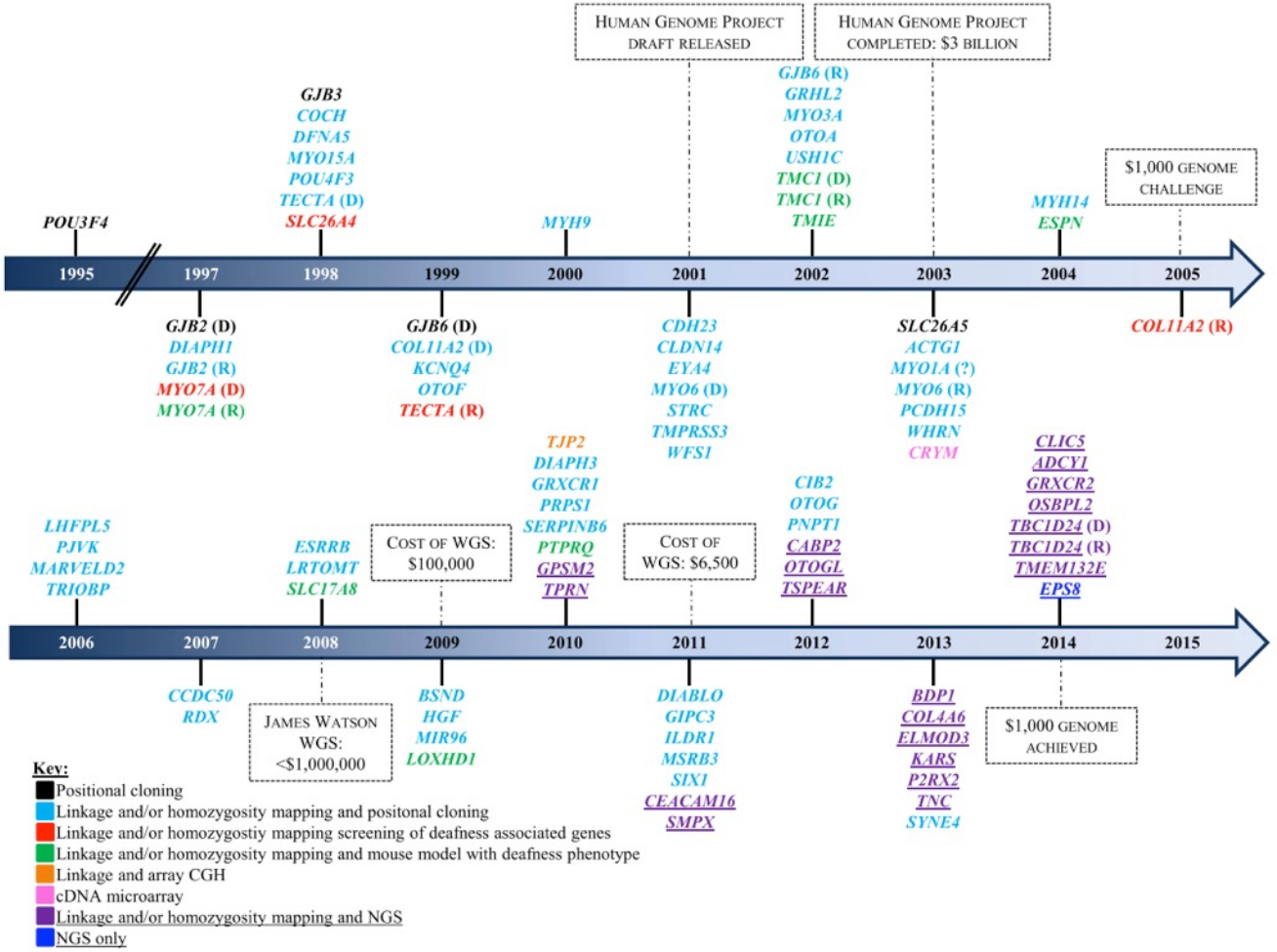


https://www.nature.com/articles/gim200764/figures/2

Genetics of Hearing Loss

- Non-syndromic hearing loss follows simple Mendelian laws
  - autosomal recessive (75-80%)
  - autosomal dominant (20%)
  - X-linked (2-5%)
  - mitochondrial (1%)

- Onset and severity also follow simple clinical patterns
  - autosomal recessive usually prelingual, non-progressive (stable) and profound
  - autosomal dominant is primarily post-lingual (onset between the 2nd and 5th decades of life) and progressive (second to third decades of life


HUMAN GENOME PROJECT DRAFT RELEASED
HUMAN GENOME PROJECT COMPLETED: $3 BILLION
$1,000 GENOME CHALLENGE
POU3F4
GJB3
COCH
DFNA5
MYO15A
POU4F3
TECTA (D)
SLC26A4
MYH9
GJB6 (R)
GRHL2
MYO3A
OTOA
USH1C
TMC1 (D)
TMC1 (R)
TMIE
MYH14
ESPN
1995
1997
1998
1999
2000
2001
2002
2003
2004
2005
GJB2 (D)
DIAPH1
GJB2 (R)
MYO7A (D)
MYO7A (R)
GJB6 (D)
COL11A2 (D)
KCNQ4
OTOF
TECTA (R)
CDH23
CLDN14
EYA4
MYO6 (D)
STRC
TMPRSS3
WFS1
SLC26A5
ACTG1
MYO1A (?)
MYO6 (R)
PCDH15
WHRN
CRYM
COL11A2 (R)
LHFPL5
PJVK
MARVELD2
TRIOBP
ESRRB
LRTOMT
SLC17A8
COST OF WGS: $100,000
TJP2
DIAPH3
GRXCR1
PRPS1
SERPINB6
PTPRQ
GPSM2
TPRN
COST OF WGS: $6,500
CIB2
OTOG
PNPT1
CABP2
OTOGL
TSPEAR
CLIC5
ADCY1
GRXCR2
OSBPL2
TBC1D24 (D)
TBC1D24 (R)
TMEM132E
EPS8
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
CCDC50
RDX
JAMES WATSON WGS: <$1,000,000
BSND
HGF
MIR96
LOXHD1
DIABLO
GIPC3
ILDR1
MSRB3
SIX1
CEACAM16
SMPX
BDP1
COL4A6
ELMOD3
KARS
P2RX2
TNC
SYNE4
$1,000 GENOME ACHIEVED
Key:
Positional cloning
Linkage and/or homozygosity mapping and positonal cloning
Linkage and/or homozygostiy mapping screening of deafness associated genes
Linkage and/or homozygosity mapping and mouse model with deafness phenotype
Linkage and array CGH
cDNA microarray
Linkage and/or homozygosity mapping and NGS
NGS only

Genetics in Hearing Loss

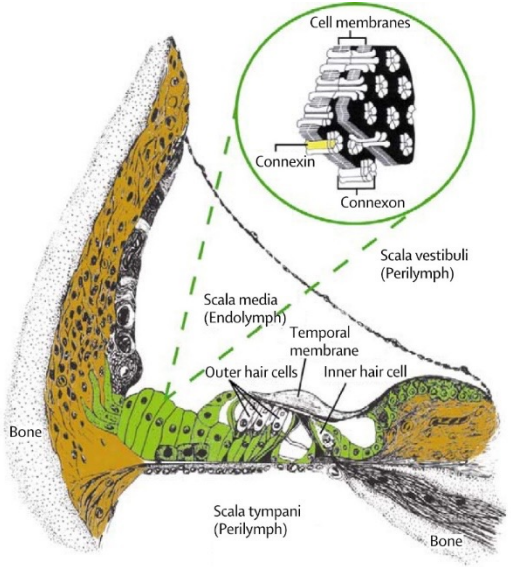
- Loci for genes inherited in an autosomal dominant manner: DFNA
- Loci for genes inherited in an autosomal recessiv manner: DFNB
- loci for genes inherited in an X-linked manner are referred: DFNX

Genes of Interest: Prevalence in Europe

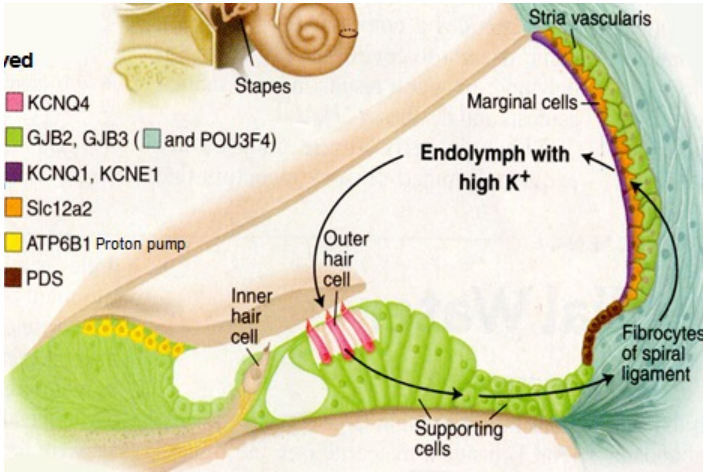
Gene	Locus	Percentage	Audioprofile
GJB2/GJB6	DFNB1	18-41%	Late onset possible; progressive
TMC1	DFNB7/11	Common in the Middle-East	Late onset with progression during first 3 decades possible
STRC	DFNB16	5.5% in GJB2-neg population	Mild to moderate, gentle downsloping
TMPRSS3	DFNB8/10	25% (arNSHI in Nijmegen)	B8 postlingual B10 prelingual

Genetic hearing loss through GJB2 mutations

Mutation Gen GJB2 → CX26 → Gap Junction → Defect Resorption K+



https://www.researchgate.net/figure/Location-of-connexin-26-GJB2-in-the-potassium-recycling-pathway-of-the-cochlea_fig4_5627377



https://www.ncbi.nlm.nih.gov/books/NBK22204/figure/connexinFig/

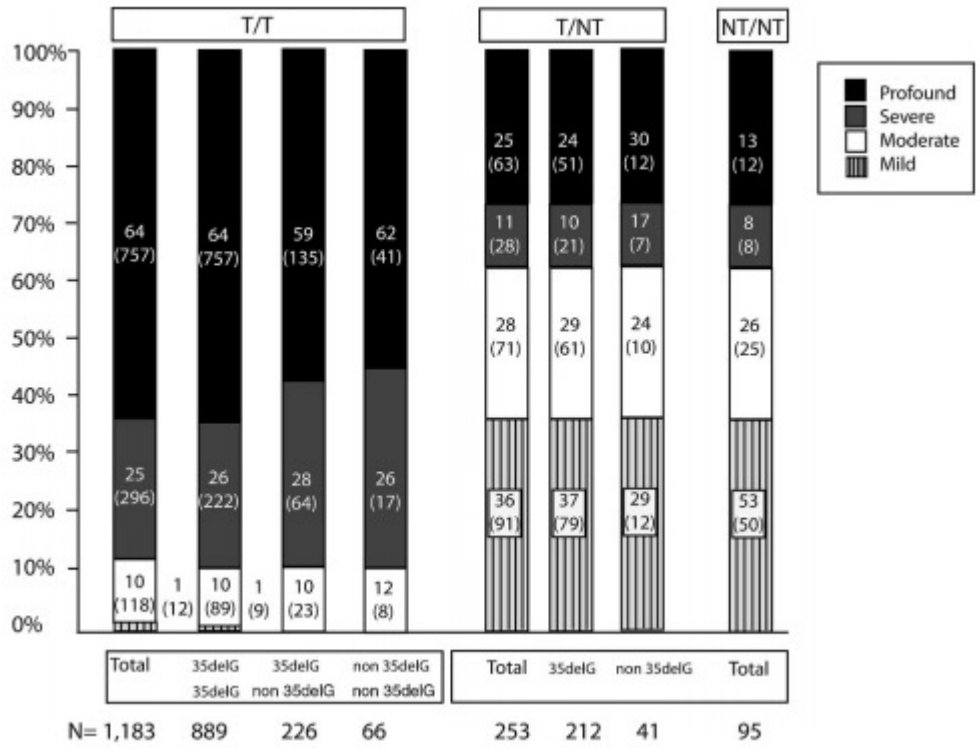
Different GJB2 Mutations

- Many mutations are either
  - biallelic *GJB2* mutations
    - mild to profound
    - most commonly nonprogressive
  - Truncating mutations (36)
    - Homozygous (T/T)
    - heterozygous (T/NT)
    - IVS1+1G→A
    - del(*GJB6-D13S1830*)

Different GJB2 Mutations

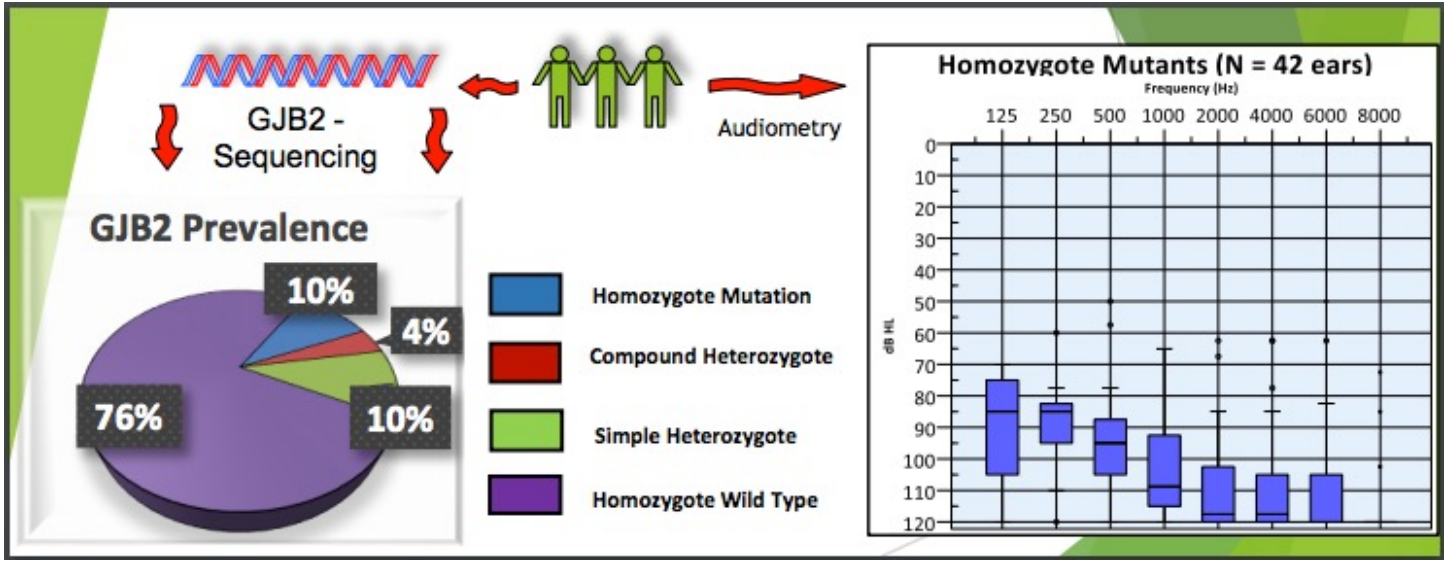
- Nontruncating mutations (47)
  - homozygous nontruncating (NT/NT)
- Heterozygous
  - M34T, Kelsell et al. 1997;
  - W44C, Denoyelle et al. 1998;
  - W44S, Gasparini et al. Personal communication;
  - R75W, Richard et al. 1998a;
  - D66H, Maestrini et al 1999

GJB2 Mutations and Grade of Hearing Loss



Kochhar, A., Hildebrand, M. & Smith, R. Clinical aspects of hereditary hearing loss. *Genet Med* **9,** 393–408 (2007). https://doi.org/10.1097/GIM.0b013e3180980bd0

GJB2 Mutations in MHH Patients



Burke WF, Warnecke A, Schöner-Heinisch A, Lesinski-Schiedat A, Maier H, Lenarz T. Prevalence and audiological profiles of GJB2 mutations in a large collective of hearing impaired patients. Hear Res. 2016 Mar;333:77-86. doi: 10.1016/j.heares.2016.01.006. Epub 2016 Jan 15. PMID: 26778469.

GJB2 Mutations in MHH Patients

First Allele	Second Allele	Number
c.35delG	c.313_326del	4
c.35delG	c.-23+1G>A	3
p.V84L	p.S139N	2
c.35delG	p.C169Y	1
c.35delG	p.S72C	1
c.35delG	p.H100Y	1
c.35delG	p.W77R	1
c.35delG	p.M34T	1
p.V153I	p.T8M	1
p.L90P	c.282C>T (p.=)	1
p.V37I	p.L90P	1
c.35delG	c.167delT	1
p.V27I	p.E114G	1
p.K15T	c.313_326del	1

Table 1: Combinations of alleles detected in compound heterozygotic form

Mutant Allele	Number
c.35delG	10
p.M34T	9
p.V153I	7
p.R127H	6
p.V27I	4
c.*3C>A	3
p.F83L	2
p.V37I	2
c.-23+1G>A	2
c.-22-2A>C	1
p.L90P	1
p.E120del	1
c.-15C>T	1
p.S139N	1
p.W24X	1

Table 2: Alleles detected in simple heterozygotic form

Burke WF, Warnecke A, Schöner-Heinisch A, Lesinski-Schiedat A, Maier H, Lenarz T. Prevalence and audiological profiles of GJB2 mutations in a large collective of hearing impaired patients. Hear Res. 2016 Mar;333:77-86. doi: 10.1016/j.heares.2016.01.006. Epub 2016 Jan 15. PMID: 26778469.

GJB2 Mutations in MHH Patients

Name of Mutation	Translated or Untranslated	Pathological?	Mutation Type	Novel?	Number of Alleles	Percent of Total Mutations
Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	825	---
c.35delG	Translated	Pathological	Frameshift	recognized	109	58.3%
p.M34T	Translated	Unknown	Missense	recognized	10	5,3%
p.R127H	Translated	Non-pathological (probably)	Missense	recognized	8	4,3%
p.V153I	Translated	Unknown	Missense	recognized	8	4,3%
c.-23+1G>A	Splice Site	Pathological	Splice Site	recognized	7	3,7%
c.313_326del	Translated	Pathological	Frameshift	recognized	5	2,7%
p.W24X	Translated	Pathological	Truncating/Nonsense	recognized	5	2,7%
p.V27I	Translated	Unknown	Missense	recognized	5	2,7%
c.*3C>A	Untranslated	Non-pathological (probably)	3' UTR	recognized	3	1,6%
p.V37I	Translated	Pathological	Missense	recognized	3	1,6%
p.S139N	Translated	Pathological	Missense	recognized	3	1,6%
p.L90P	Translated	pathological	Missense	recognized	3	1,6%
p.F83L	Translated	Non-pathological (probably)	Missense	recognized	2	1,1%
c.299_300delAT	Translated	Pathological	Frameshift	recognized	2	1,1%
p.V84L	Translated	Pathological	Missense	recognized	2	1,1%
p.S72C	Translated	Pathological (probably)	Missense	recognized	1	0.5%
c.-22-2A>C	Splice Site	Pathological	Splice Site	recognized	1	0,5%
p.K15T	Translated	Pathological (probably)	Missense	recognized	1	0,5%
p.E114G	Translated	Unknown	Missense	recognized	1	0,5%

GJB2 Mutations in MHH Patients

p.T8M	Translated	Pathological	Missense	recognized	1	0,5%
c.282C>T (p.=)	Translated	Non-pathological (probably)	silent	recognized	1	0,5%
p.H100Y	Translated	Pathological	Missense	recognized	1	0,5%
c.-15C>T	Untranslated	Non-pathological (probably)	Intronic	recognized	1	0,5%
p.E120del	Translated	Pathological	in frame deletion	recognized	1	0,5%
c.167delT	Translated	Pathological	Frameshift	recognized	1	0,5%
p.C169Y	Translated	Pathological (probably)	Missense	recognized	1	0,5%
p.W77R	Translated	Pathological	Missense	recognized	1	0,5%

Table 3: Overview of mutations detected and their overall prevalences in the cohort

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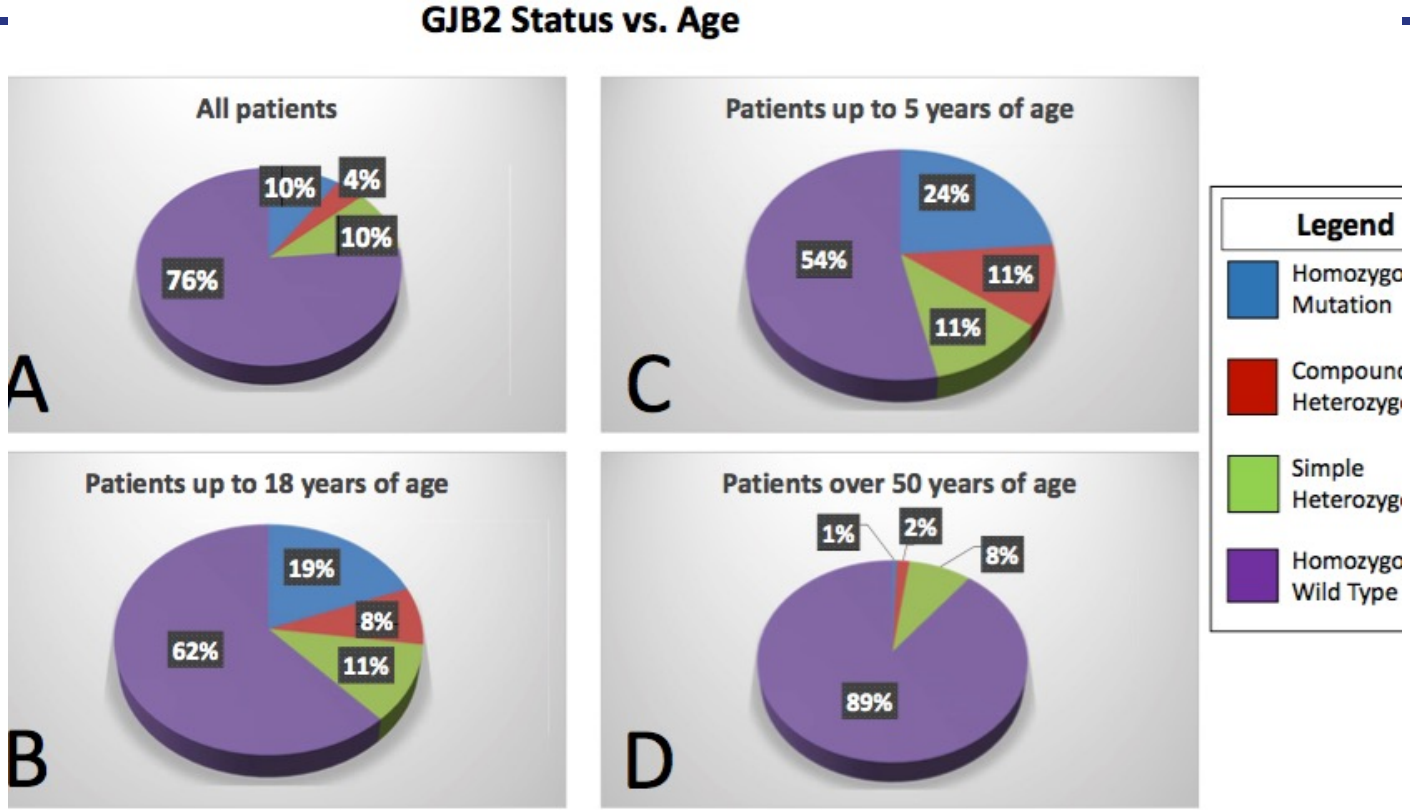

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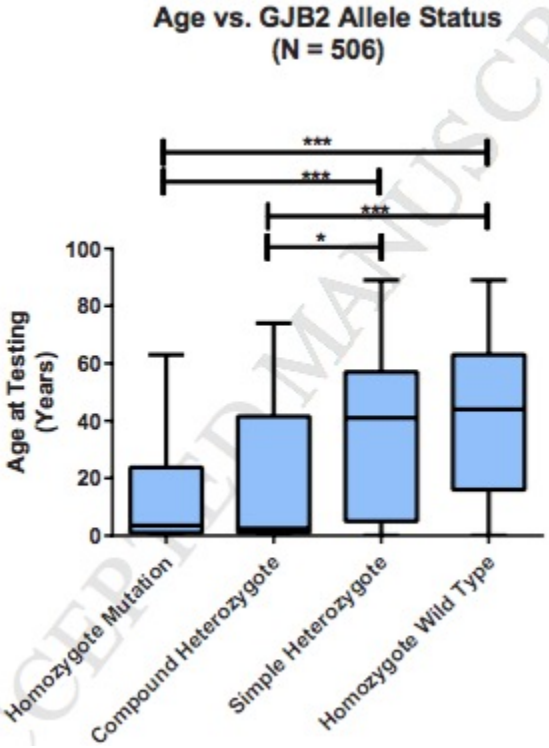
GJB2 Mutations in MHH Patients



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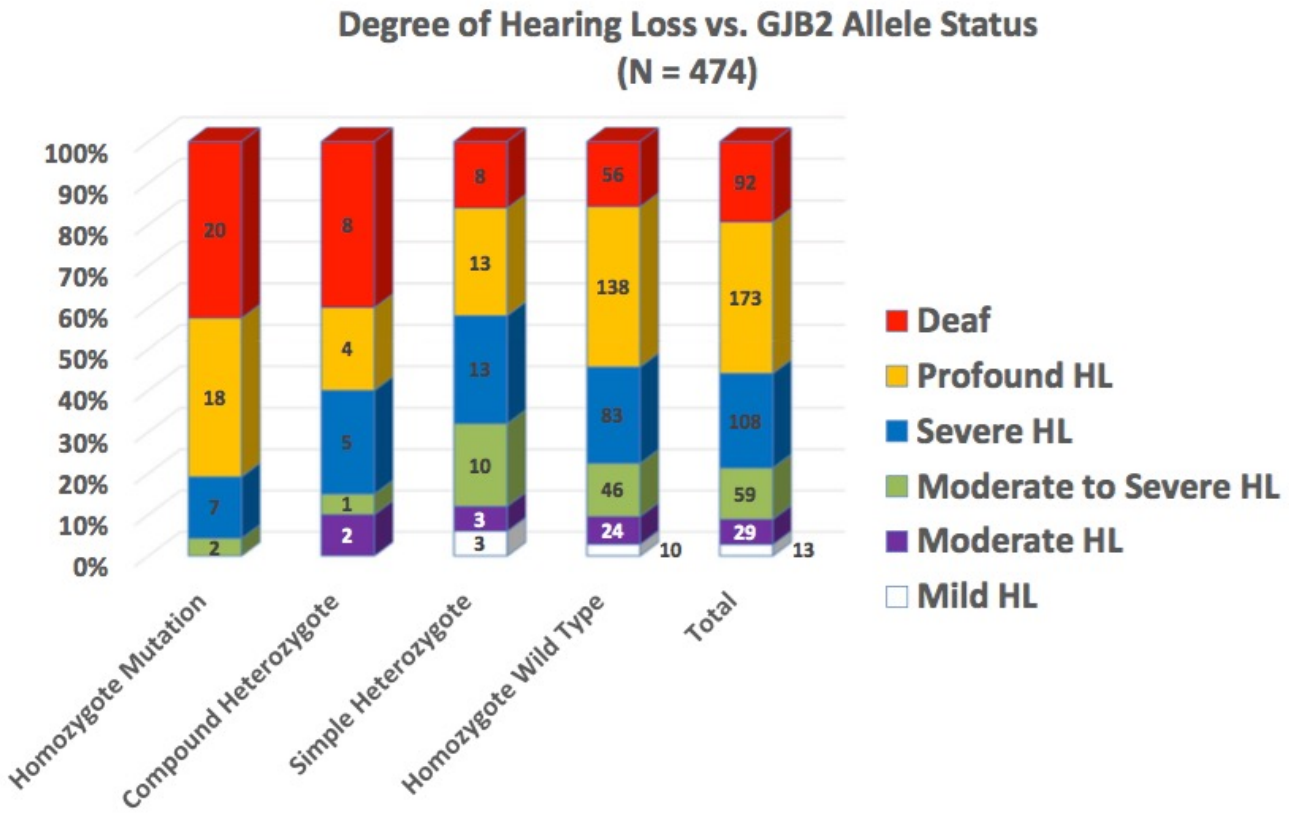
GJB2 Mutations in MHH Patients



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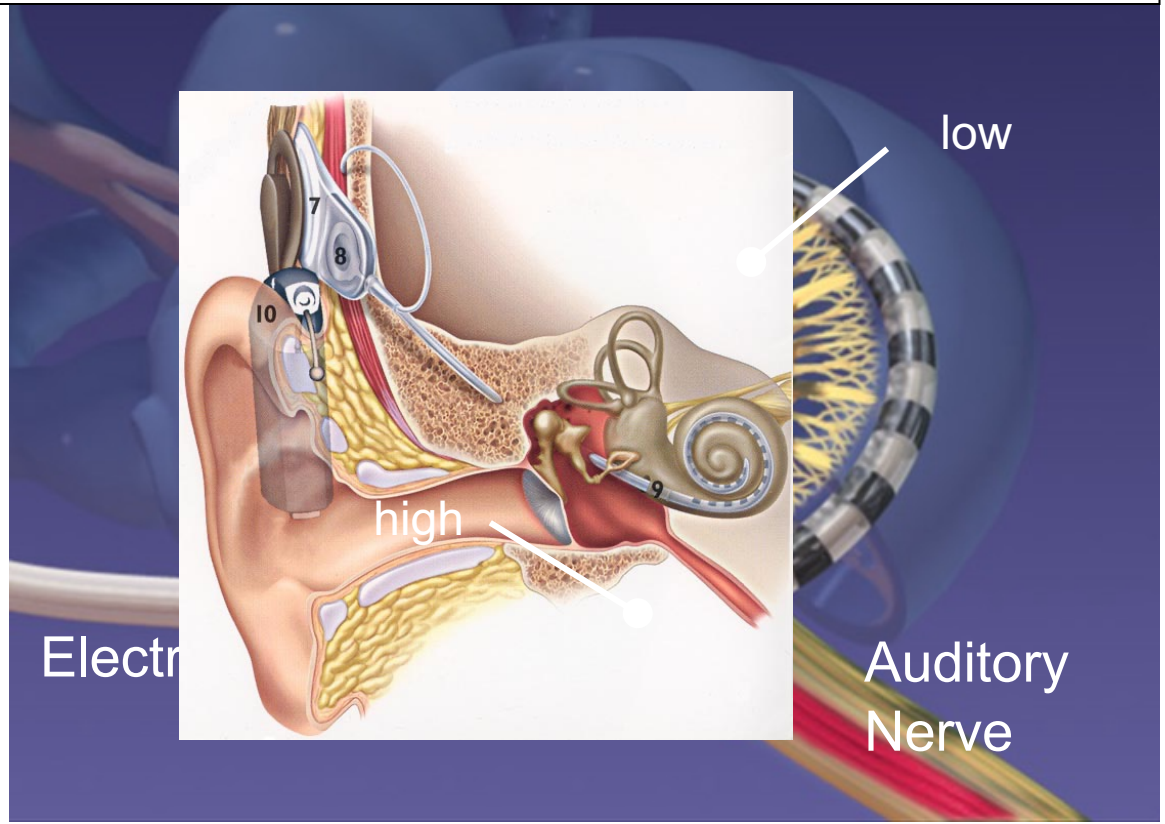
Treatment for GJB2 Gene Related Hearing Loss

- Hearing Devices
  - Depending on the grade of hearing loss
  - Hearing Aids
  - Cochlear Implants

- Future
  - Gene Therapy

Cochlear Implant



GJB2 Mutations Therapy with CI

TABLE 1. *Criteria in the Speech Intelligibility Rating scale used to categorize children*

Category	Speech intelligibility criteria
1	Connected speech is unintelligible. Prerecognizable words in spoken language, primary mode of communication may be manual.
2	Connected speech is unintelligible. Intelligible speech is developing in single words when context and lip-reading cues are available.
3	Connected speech is intelligible to a listener who concentrates and lip-reads.
4	Connected speech is intelligible to a listener who has a little experience of a deaf person's speech.
5	Connected speech is intelligible to all listeners. Child is understood easily in everyday contexts.

Sinnathuray, Arasa Raj*†; Toner, Joseph G.*; Clarke-Lyttle, Joanne*; Geddis, Andrea*; Patterson, Christopher C.‡; Hughes, Anne E.† Connexin 26 (GJB2) Gene-Related Deafness and Speech Intelligibility After Cochlear Implantation, Otology & Neurotology: November 2004 - Volume 25 - Issue 6 - p 935-942

GJB2 Mutations Therapy with CI

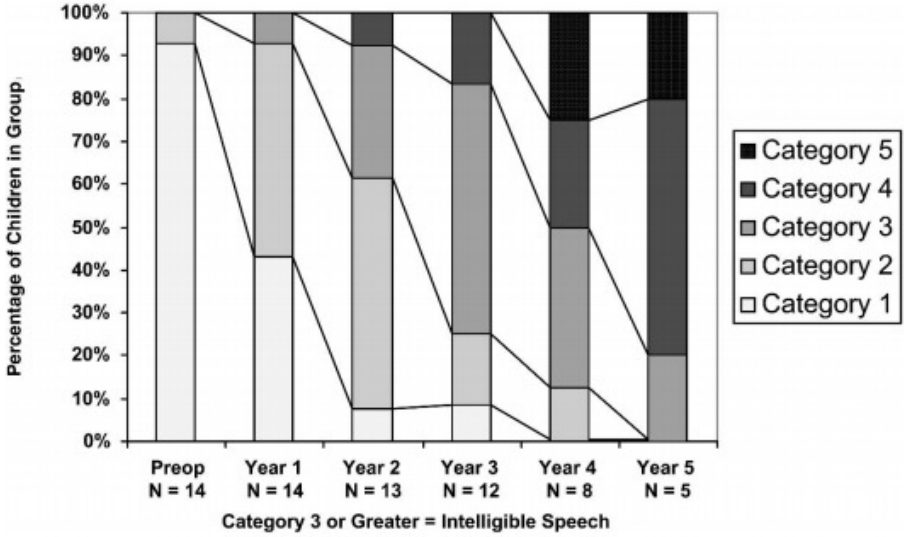


FIG. 1. Trends of improving SIR scores in patients with *GJB2*-related deafness, before and up to 5 years after implantation. At Year 3, the only child who scored in Category 1 has developmental verbal dyspraxia.

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Gene Therapy

1. Gene therapy may be suitable for some of the genetic conditions but not for all

2. Differentiating between recessive and dominant disease is also important when considering gene therapy for GJB2 mutations

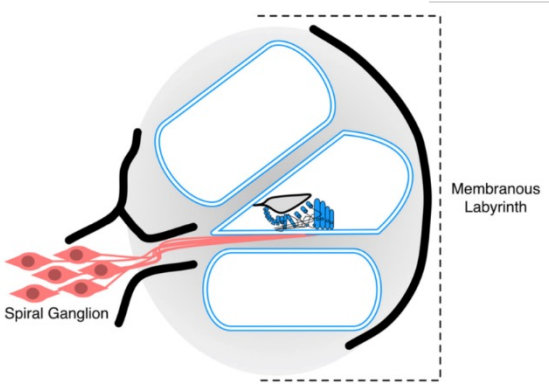
Bildquelle: MHH HNO

Gene Therapy for Hearing Loss

- Genetic therapy consists of the delivery of genes into the inner ear
- Delivering genes with viral vectors is potentially the most efficient method.

- Limitations
  - potential immune response
  - lack of access to the scala media
  - variability in the outcome
  - lack of specificity to the type of cell transduced.

Gene therapy in Genetic Hearing Loss



GJB2
SLC26A4
OTOF
LOXHD1
KCNQ1
CDH23
MYO7A
POU3F4
MYH9
TMC1

COCH

TMPRSS3
CHD7

DDP1/TIMM8a

Eppsteiner et al., 2002

- Preserveation of residual hearing
- Protection of spiral ganglion neurons
- Adeno-associated viruses for cell-specific targeting
- Identification of patients suitable for gene therapy

Microstructure of the cochlea with cells affected by gene mutations and their incidence

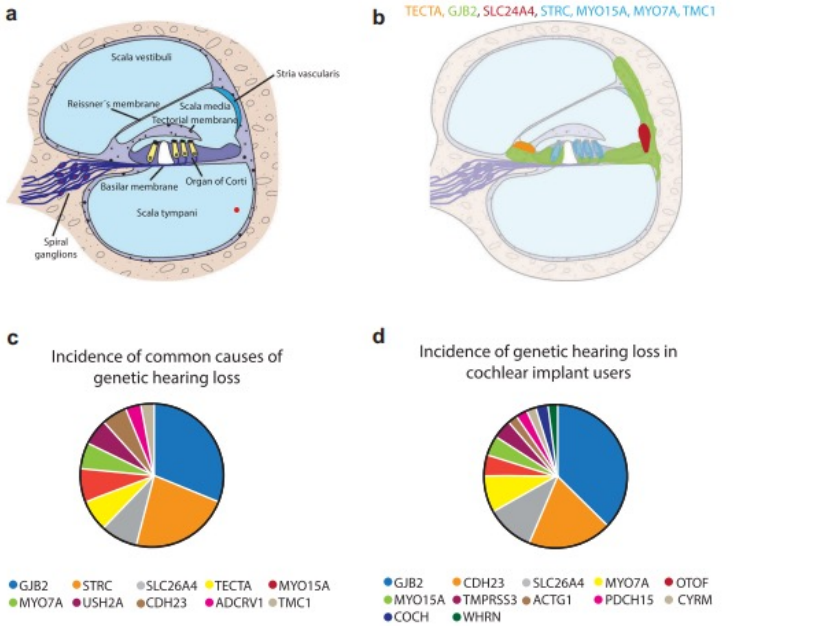
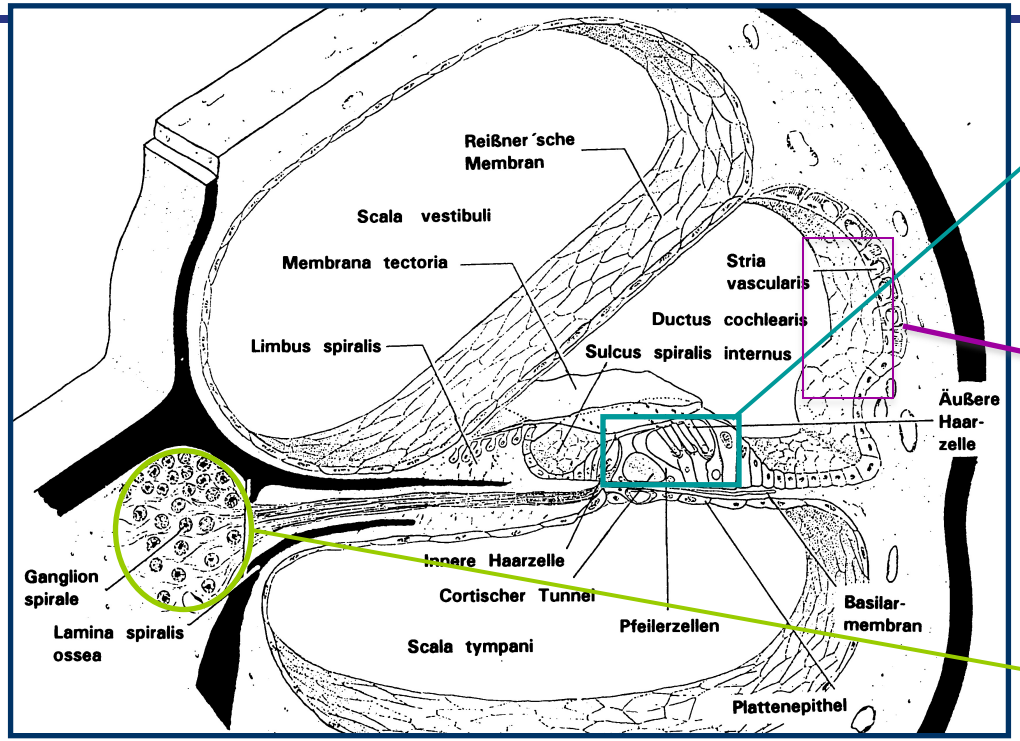
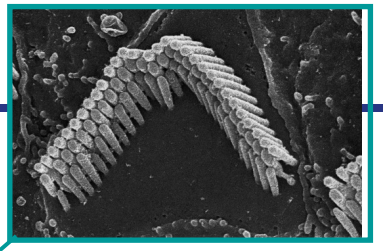


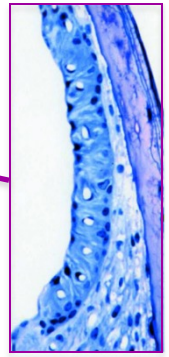
Figure 2. Microanatomy of the human inner ear with distribution of common genes causing hearing loss. The inner ear has a diverse population of cells that play different and important roles in hearing (a). The sensory hair cells (one row of inner and three rows of outer hair cells are marked in yellow). The cells need to be individually targeted with vectors/tissue-specific promoters to achieve optimal results. Distribution of the 7 most common causes of genetic hearing loss shows that different areas of the inner ear are affected (b). There are differences in the incidence of genes causing hearing loss in the general population (c), and a cochlear implant population (d). The distribution and incidence of the targeted gene need to be taken into account when translating animal research to human studies (Illustrations shown are based on data from [6,7,21]).

Targeted Gene Therapy

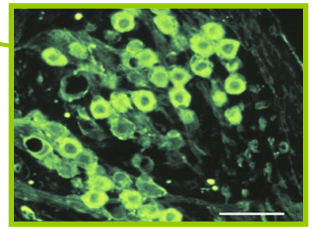




Hair cells

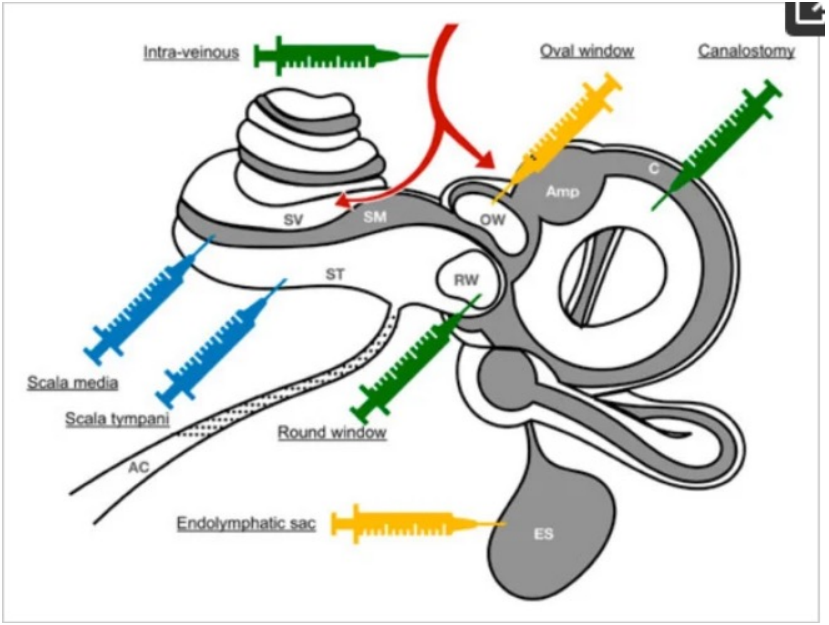


Stria vascularis



Spiral ganglion neurons

Application Routes to the Inner Ear



Blanc, Fabian; Mondain, Michel; Bemelmans, Alexis-Pierre; Affortit, Corentin; Puel, Jean-Luc; Wang, Jing. 2020. "rAAV-Mediated Cochlear Gene Therapy: Prospects and Challenges for Clinical Application" *J. Clin. Med.* 9, no. 2: 589. https://doi.org/10.3390/jcm9020589

Outlook on Gene Therapy for Hearing Loss

- Gene therapeutic approaches will be available for almost all autosomal recessive diseases in the near future

- Gene therapy approachs concentrate on adeno-, adenoassociated- and lentiviral vectors

- Identification of clinically relevant groups as candidates for timely gene therapy is currently a high priority in otology

Thank you for your attention

SENSORION PORTFOLIO

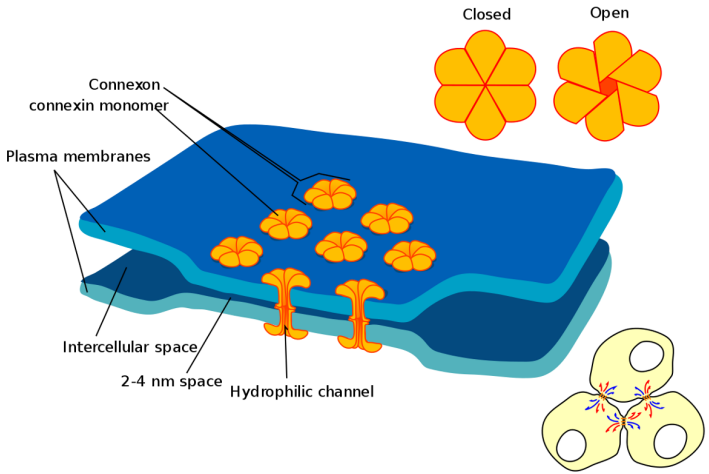
Focus on GJB2 program

Sensorion

Pipeline: Building an attractive pipeline in the hearing space

3SBio has a right of first refusal with respect to licensing in Greater China of SENS-401 (except in combination with cochlear implants), OTOF-GT and USHER-GT
**Option to obtain a licence from Institut Pasteur (pre-defined financial terms and other terms to be negotiatied)*

Connexin 26: A gap-junction protein encoded by GJB2 gene and responsible for tissue homeostasis Mutation in the gene leads to deafness



- **GJB2** is the gene encoding for the **Connexin 26** protein; one of 20 known connexins in humans and almost endemic to the cochlea (together with Cx30).
- Gap Junctions are **key for the intercellular exchange of molecules.**
- GJB2 mutations are the most prevalent form of congenital deafness (DFNB1).
- Severity varies from mild to profound with hearing loss occurring typically in the higher range of frequencies but all are affected [1].
- Children are usually being diagnosed during the newborn screening routine and current SoC is cochlear implantation prior language acquisition.

[1] Kenneson et al. 2002

We estimate that GJB2 related hearing loss affects ~ 300,000 patients in the US and EU

We have identified 3 forms of hearing loss associated with GJB2 gene mutations (Connexin 26).

Prevalence of Congenital and Childhood onset forms estimated to be around 200k patients and around **50% of autosomal recessive non syndromic hearing loss cases are thought to be from GJB2 mutations.**

CONGENITAL	• Congenital hearing loss due to GJB2 mutations is typically severe to profound[1] • ~80% of hearing loss cases due to GJB2 mutations in children are thought to be congenital.
CHILDHOOD ONSET	• Estimates are that ~20% of cases feature a late onset (during childhood) progression of hearing loss. • The onset becomes more severe around 6 years old and continues[2].
EARLY ONSET OF PRESBYCUSIS	• ~100k patients between 30 and 69 years old thought to be affected by a monogenic form of presbycusis due to GJB2 mutations.

[1]: Snoeckx al. 2005; [2]: Discussions with KOL at Necker Hospital

Cx26 is a good candidate for gene therapy

Why CX26 is a good candidate?

- More than 100 recessive mutations origin Cx26 truncation/ deletion leading to nonsyndromic hearing loss and deafness (DFNB1).
- Partial loss (compound heterozygous or truncated proteins) causes hearing loss [1].
- cDNA = 2,318 bp compatible with the use of one AAV.
- Correct expression and localization of the protein (~50%) with restored GJ intercellular network [2].

Key parameters to consider

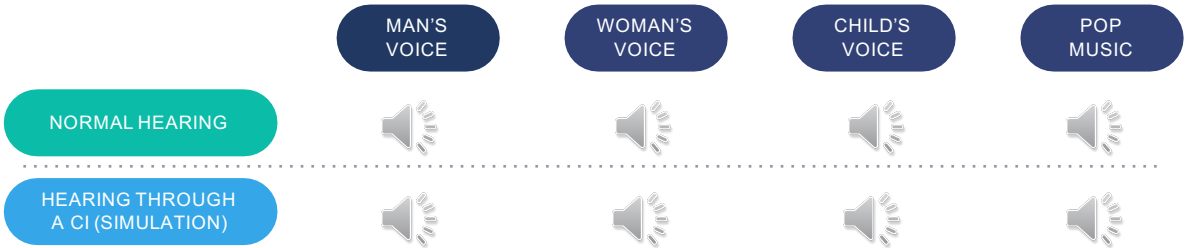
- **Age of mice:** Use conditional-inducible Cx26-/- mice to better mimic the intended intervention into human.
- **Mutation:** Mouse models with human predominant mutations.
- **Vector design:**
  - Promoter: Optimal structure (enhancers) for expression restricted to epithelial and connective tissues.
  - Vector: De-target hair-cells (especially outer hair cells).

[1] Fetoni *et al.*, Redox Biol. 2018 - [2] Yu *et al*, 2014

Value proposition for restoring natural hearing with gene therapy

- **Acoustic hearing:** High frequency resolution (20-20.000 Hz) allowing to enjoy music and complex sounds.
- **Cochlear implants:** Use 8-22 electrodes resulting in artificially distorted signal.
- **Spatial hearing:** Humans can identify the direction of a sound source. Even with two devices, cochlear implants are likely not allowing spatial hearing.
- **Gene Therapy is aiming at restoring natural acoustic hearing.**

How does hearing with a cochlear implant sound?



Next steps

Aim: Restoration/reversion, at minima safely stop disease progression

1. Natural History Study in collaboration with the research and innovation center of Necker Hospital: Study patient phenotypes to deepen the knowledge of the patients' profile (genetics, phenotype, disease progression)
2. Design an accurate promoter and test promoter / capsid in Non Human Primates
3. Preclinical IND enabling studies

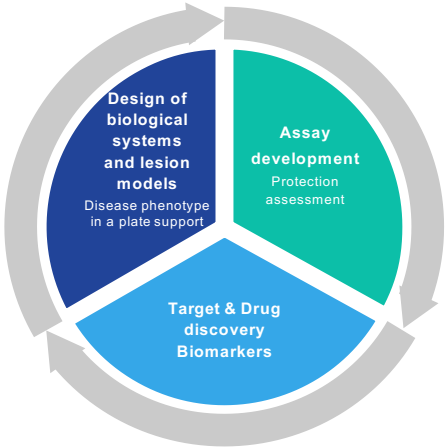
SENSORION CAPABILITIES

Sensorion

Sensorion HQ in Montpellier

- Sensorion was founded in 2009 as a Spin-Off from INSERM.
- Moved to SANOFI Campus in 2015:
  - SANOFI R&D Center was built in 1972.
  - Hosting >1000 employees.
  - Fully integrated development site for small molecules and biologics.
  - Spare capacity is rented out to 10 external companies.

We are continuously strengthening our in vitro / in vivo platforms



Invitro

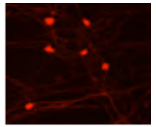
Cellular Assays — Primary culture of the main cochlear cell types, live imagin

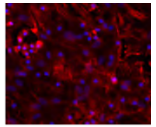
Tissular Assays — *ex vivo cochlear* explant cultures, live imaging

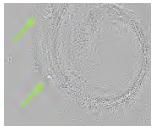
Electro-physiology — Neural electric activity modulation assays

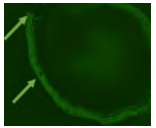
Ganglion neurons

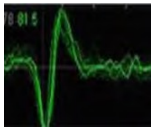
Spiral ligament fibrocytes

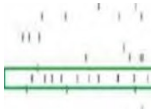








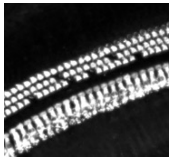




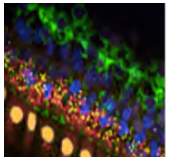
Invivo

Candidate Drug Identification — Advanced imaging techniques to measure cell/synapse protection and regeneration potential

Auditory Brainstem Response (ABR) and Distortion Product of Otoacoustic Emissions (DPOAEs)



Hair cell survival (cochleogram)



Synaptic integrity (pre/post synaptic)

We use our Gene Therapy screening platform to select the best candidate for expression specificity

In Silico Promoters and Plasmids Design

- Transcription Factor Binding Motif
- Enhancers, silencers
- Promoter/Plasmids design

- Inner ear cell-specific promoters design
- Plasmids design
- Optimal expression of genes of interest

In vitro Cell Assays

- Cell transfection
- Cell infection
- RT-qPCR
- Western blot Analysis

- Transcription efficacy of cell-specific and synthetic promoters in cell lines

Ex vivo Studies

- Cochlear Explants
- Ex vivo Electroporation

- Efficient GFP overexpression from candidates promoters in targeted cell populations in cochlear explants

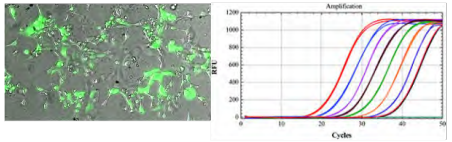
Ex vivo screening

- Viral Infection of cochlear
- Ex vivo AAV capsids screening

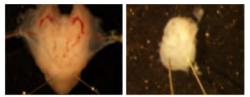
- Multiplexed screening of AAV capsids
- Automated cell imaging and transduction quantification

Promoter Design

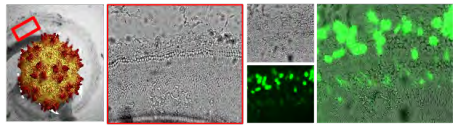
Cellular Assays



Electroporation of embryonic cochlear explants



Viral Infection of Postnatal cochlear explants

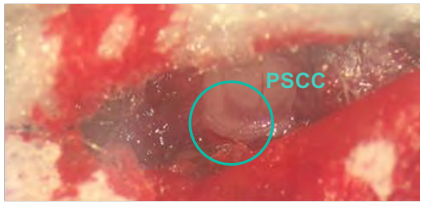


Our in-vivo gene therapy platform enables us to test different techniques

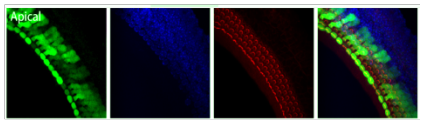
Microsurgery of the inner ear	• Canalostomy of the posterior semi-circular canal (PSCC) Round window membrane injection	• Optimization of the inner ear gene delivery techniques in rodents and disease models
In Vivo Viral Infection of the inner ear	• Injection of AAVs into the inner ear using RWI or canalostomy techniques	• Efficient transduction of the inner ear cell populations
In vivo capsid screening	• In vivo Screening of AAV capsids	• Identification of cell specific AAV capsids suitable for the inner ear transduction
Structural and histologic analysis of the inner ear	• Cryosections of the inner ear • Whole mount immunostaining using inner ear cell markers	• Evaluation of tropism and efficacy of AAVs in the inner ear

Round window (RW) injection

Canalostomy of the Posterior Semi-Circular canal



In Vivo AAV injection into the inner ear



Understanding deeply the manufacturing process is critical

CF5 – CF10

2L – 10L

50L

50L

200L

RESEARC

- Vector Genome titer (vG)
- SDS-page
- Endotoxin level

- Vector design
- Proof-of-concept

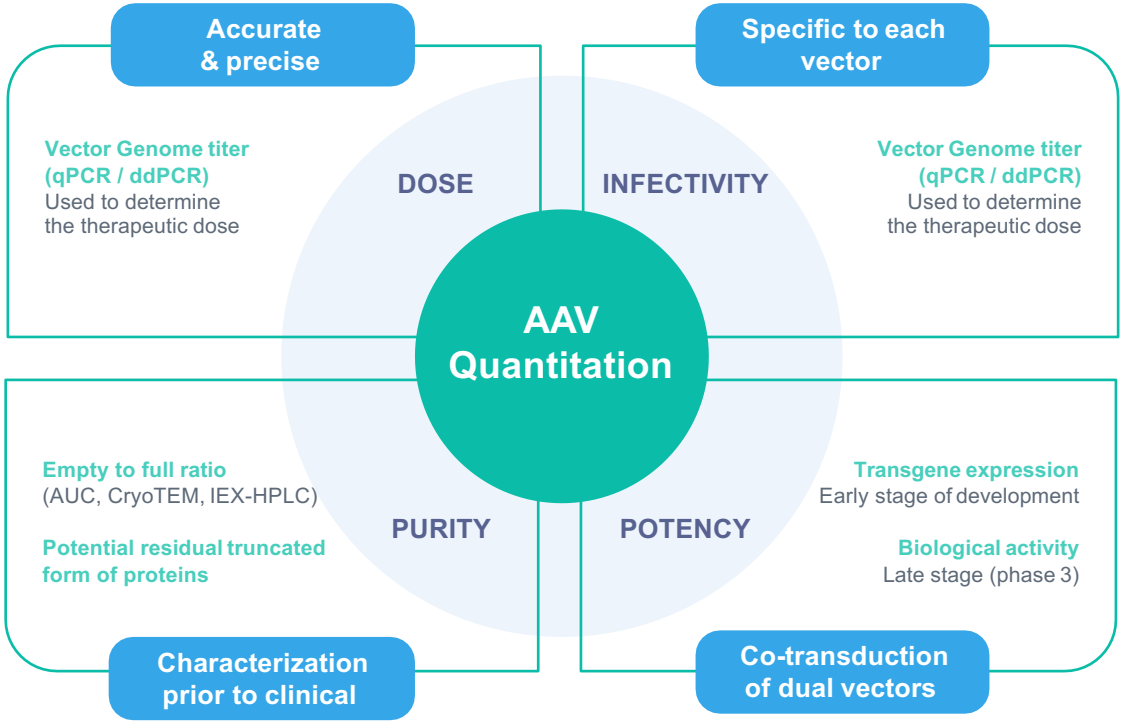
PROCESS DEVELOPMENT AND SCALE UP

- DoE at small scale for optimizing conditions
- CPPs identification
- Process adjustment
- Reference standard material
- Dose-finding study

NON-GMP & GMP MANUFACTURIN G

- Process adjustment
- Master cell banks (or working CB) & HQ-grade plasmids
- Stability studies
- Toxicological and biodistribution studies
- Clinical studies

We are developing internally the AAV quantification assays to measure our key product attributes



The platforms developed within Sensorion are critical for the successful development of our programs

Preclinical GT facilities

- **AAV Screening platform:** Design and select the best drug candidate according to the target indication
- **In vivo gene therapy platform:** From the PoC to the dose-finding studies

CMC GT Facilities

Process development lab

- Laboratory implementation (small scale)
- Non-GMP manufacturing at small scale: Set-up a platform for AAV productions from 250 mL up to 3L in bioreactor

Analytical development lab

- Development of product-specific methods hOTOF: VG titer assays achieved and gene expression assay
- Generic methods: Internalize generic assay to support process development and AAV productions

Sensorion is continuously improving its capabilities to become a leading gene therapy player

- Experienced management team with broad expertise in gene therapy.
- Established canalostonomy and RWI techniques enable efficient and safe delivery with potent transduction of inner ear cells.
- Proprietary AAV / capsid screening platforms enable optimal protein expression.
- In-house analytics and CMC platform.
- Delivering high-quality gene therpy products from research to GMP grade.

THANK YOU

Sensorion