THE PATHOPHYSIOLOGY OF SENSORINEURAL HEARING LOSS

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Hearing loss

- Hearing impairment is the most frequent sensory deficit in human populations, affecting 440 million people worldwide.
- Several studies have demonstrated that hearing loss is associated with a greater risk of cognitive impairment.
- Listed by the World Health Organization as a priority disease for research into therapeutic interventions to address public health needs.

Vestibular loss

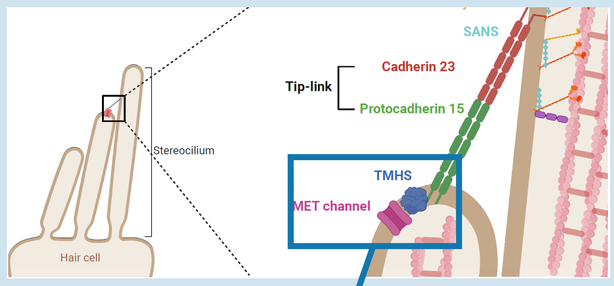
- Commonly associated with hearing loss, can be caused by meningitis, toxic medication or genetic disorders.
- Characterized by an abnormal vestibular ocular reflex (VOR) and oscillopsia.
- Impact on daily life is often underestimated.
- Patients have a high risk of falling and have difficulties with spatial orientation.
- Currently no therapy available.

DFNA9

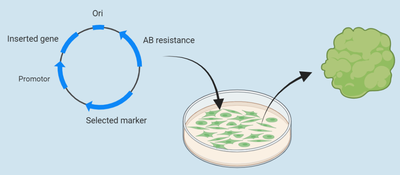
- DFNA9 (DeaFNess Autosomal 9) is an autosomal dominant disorder characterized by hearing and vestibular loss.
- Age of onset is between the 3th and 5th decade of life.
- Caused by mutations in the *COCH* gene. p.P51S mutation is common in Belgium and The Netherlands.
- Currently no treatment available to stop or prevent the hearing and vestibular loss.

Unravelling the auditory mechanism

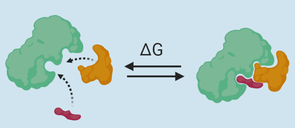
Identification of novel components of the mechanosensory transduction channel via **single cell proteomics** and **AP-MS**



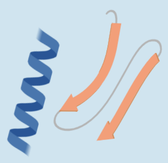
Production protein complex



Characterization interactions

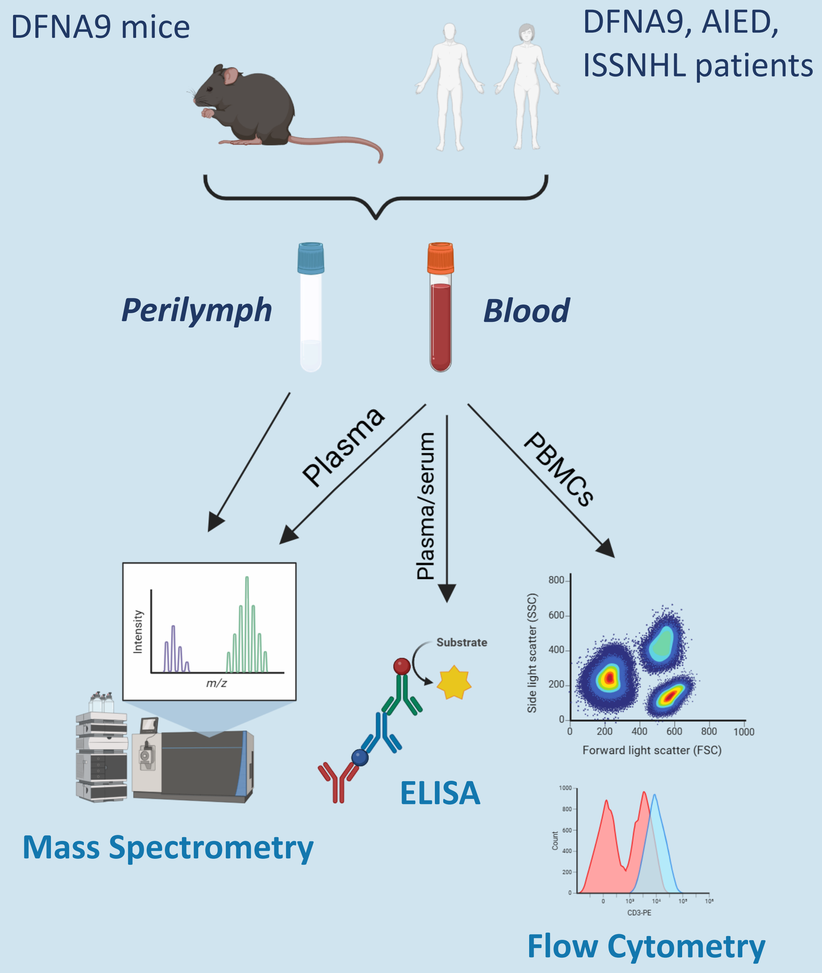


Structure determination



Validation interaction via AP-MS

Biomarkers for SNHL



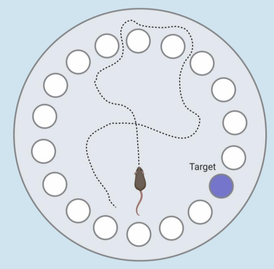
Mass Spectrometry

ELISA

Flow Cytometry

Behavioural Assessment in DFNA9

Hearing (and vestibular) loss is a modifiable risk factor for accelerated cognitive decline – cognitive function of DFNA9 patients might be affected.

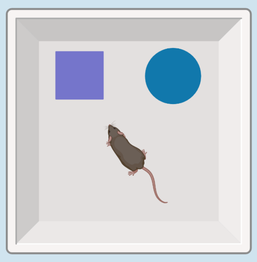


Barnes Maze – spatial learning and memory

Evaluation of hippocampal-dependent visual-spatial learning and long-term memory. The circular platform leads to one hole, the escape box. The mice are trained to find the escape box relying on spatial cues around the arena.

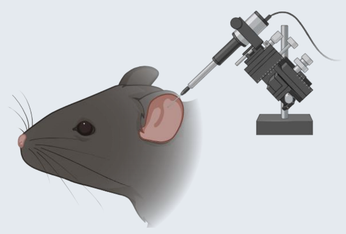
Novel Object Recognition Test – non-spatial learning and memory

Evaluation of differences in the exploration time of novel and familiar objects in an open-field environment and assess (non-spatial) hippocampal-dependent learning and memory.



Therapy to prevent DFNA9

Humanized DFNA9 mouse model

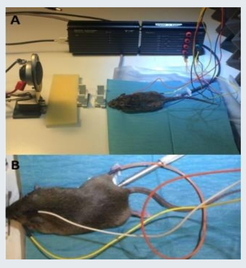


CRISPR/Cas9

Antisense oligonucleotides (ASOs)

Hearing function

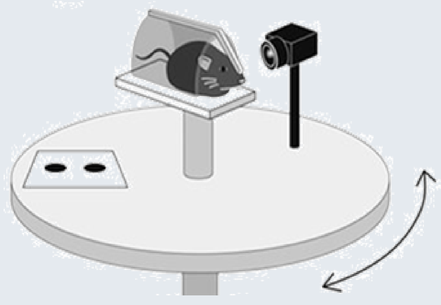
a) ABR



b) DPOAE

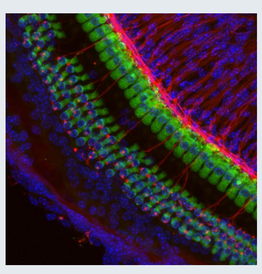
Vestibular function

c)



Immunohistochemistry

d) Organ of Corti



e) Spiral ligament

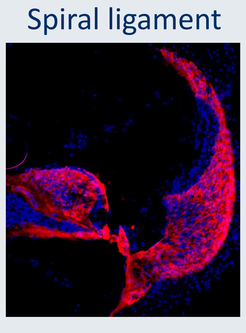
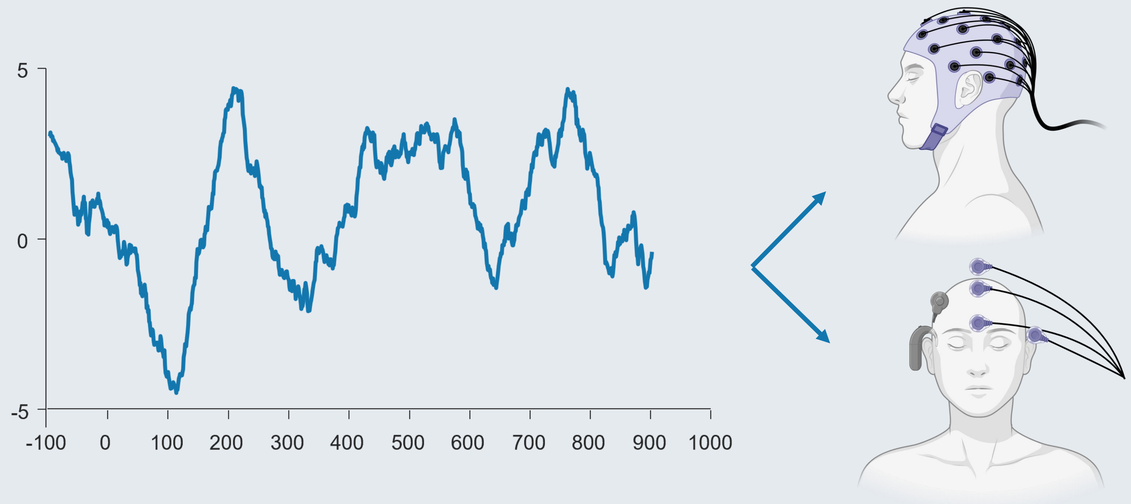


Fig 1. **(a)** Auditory Brainstem Response (ABR) set-up **(b)** Distortion Product Otoacoustic Emissions (DPOAE) set-up **(c)** Vestibular Ocular Reflex set-up **(d)** Immunofluorescence of the Organ of Corti. Hair cells are represented in green, neurons are represented in red **(e)** Immunofluorescence of the spiral ligament. *Coch* protein is stained using an anti-*Coch* antibody.

Acoustic Change Complex

Objective measure to predict hearing function



Normal hearing and hearing loss

- Objective speech in noise prediction with EEG measurements
- Localization of the ACC neural generators in the brain

Cochlear implant (CI)

- Gain insight into auditory processing in CI users
- Distinguish brain activity from the electrical artefact generated by the CI

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