# PATHOPHYSIOLOGY OF SENSORINEURAL HEARING LOSS IN AN ANIMAL MODEL

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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

- Common associated with hearing loss, can by caused by meningitis, toxic mediation 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.

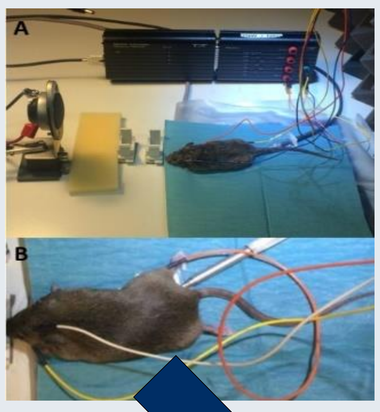
## DFNA9

- 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..

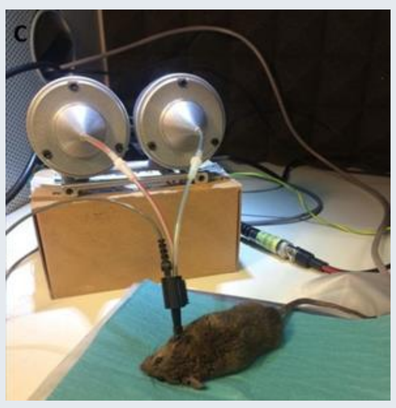
# METHODS

## Hearing function

### ABR




### DPOAE



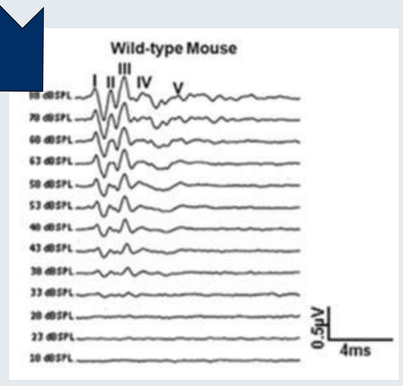
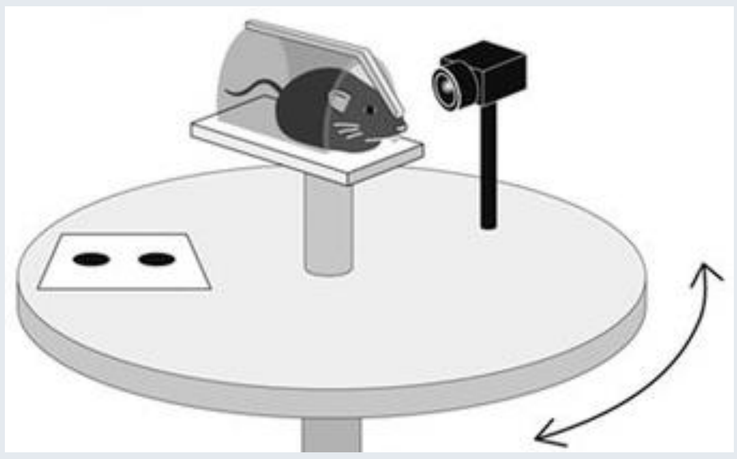



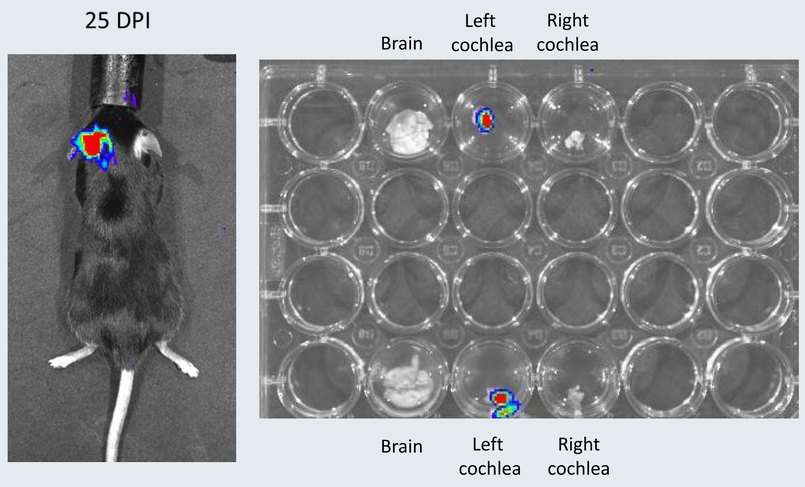

Fig 1. ABR tracings from a wildtype mouse.

## Vestibular function

### Vestibular Ocular Reflex



## Bioluminescence imaging




## Immunohistochemistry

### Organ of Corti

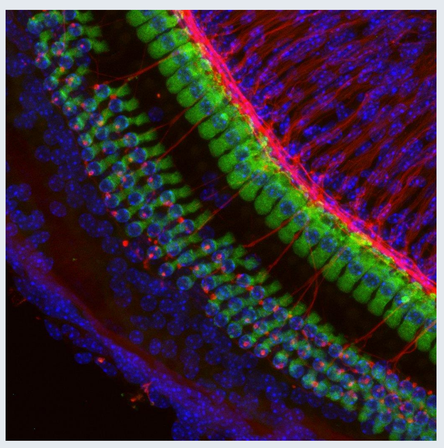


Fig 2. Immunofluorescence of the Organ of Corti. Hair cells are represented in green, neurons are represented in red.

### Spiral ligament



Fig 3. Immunofluorescence of the spiral ligament. *Coch* protein is stained using an anti-*Coch* antibody.

# DFNA9 PATHOLOGY

### Mutations in the *COCH* gene

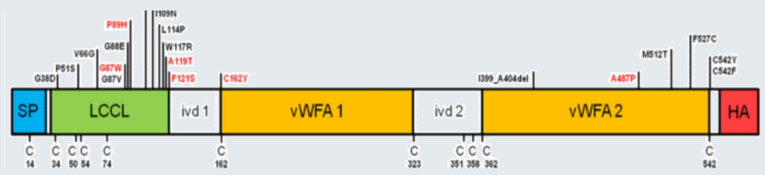



Fig 4. Different mutations in the *COCH* gene causing DFNA9.

### Misfolding and accumulation of *COCH* protein in the spiral ligament and spiral limbus of the inner ear

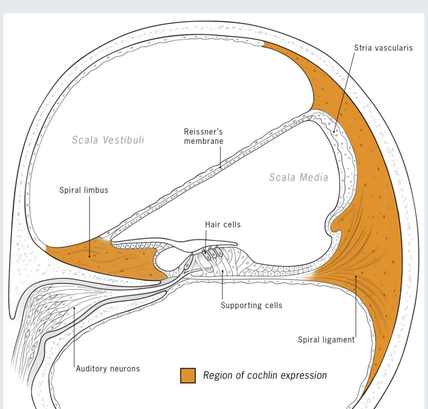



Fig 5. Regions of cochlin expression in the inner ear are indicated in orange. These regions include the spiral ligament and spiral limbus.

# ONGOING RESEARCH

### Gene therapy to prevent DFNA9

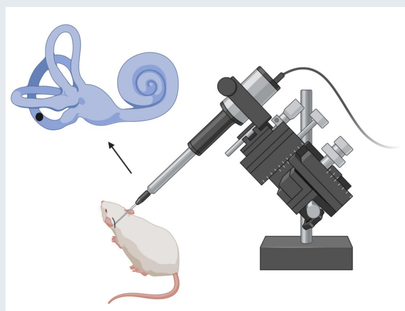
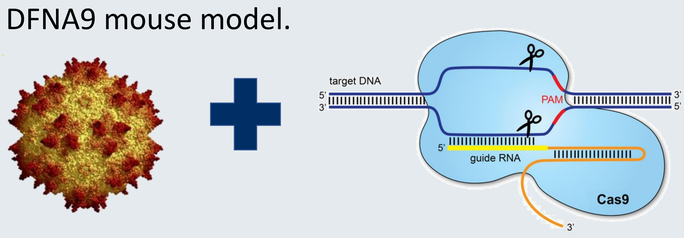


Fig 6. Injection through the posterior semicircular canal.

- Viral or non-viral vector carrying the CRISPR nuclease will be injected through the posterior semicircular canal of the DFNA9 mouse model.




- Disruption of the mutant *COCH* allele by the CRISPR nuclease will prevent misfolding and accumulation of the *COCH* protein.

# HUMANIZED MOUSE MODEL

- Mice carrying the P51S mutation causing DFNA9 in Belgium and The Netherlands.
- Hearing loss expected to start at 15 months, vestibular loss expected to start at 11 months.
- Represents the Dutch and Belgian DFNA9 patient population.

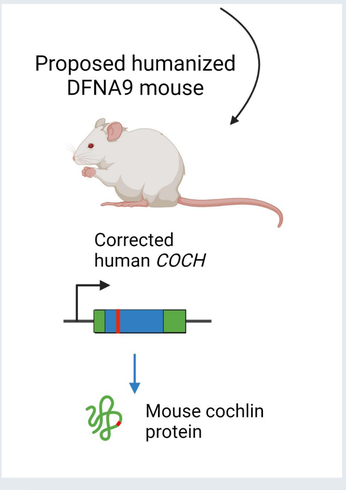




Fig 7. Humanized DFNA9 mouse model carrying the p.P51S mutation.

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