

The background of the slide is white and covered with a pattern of yellow ear emojis. The ears are scattered across the entire surface, some appearing in sharp focus while others are blurred, creating a sense of depth. They are oriented in various directions, some facing left and some right.

James Arwyn-Jones

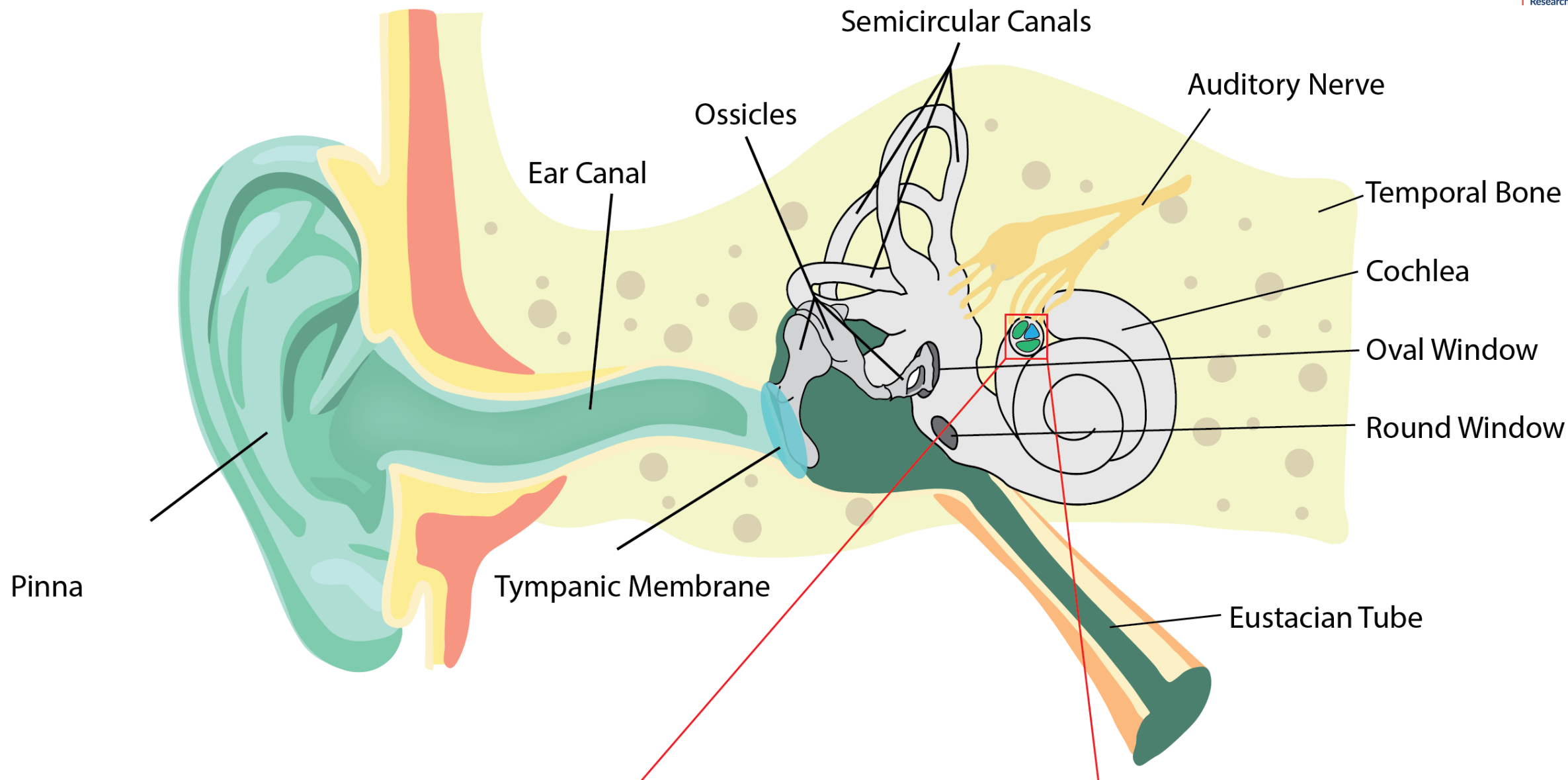
Lewis Spitz Surgeon-Scientist PhD Fellow
Prof Jane Sowden Group
Great Ormond Street Institute of Child Health

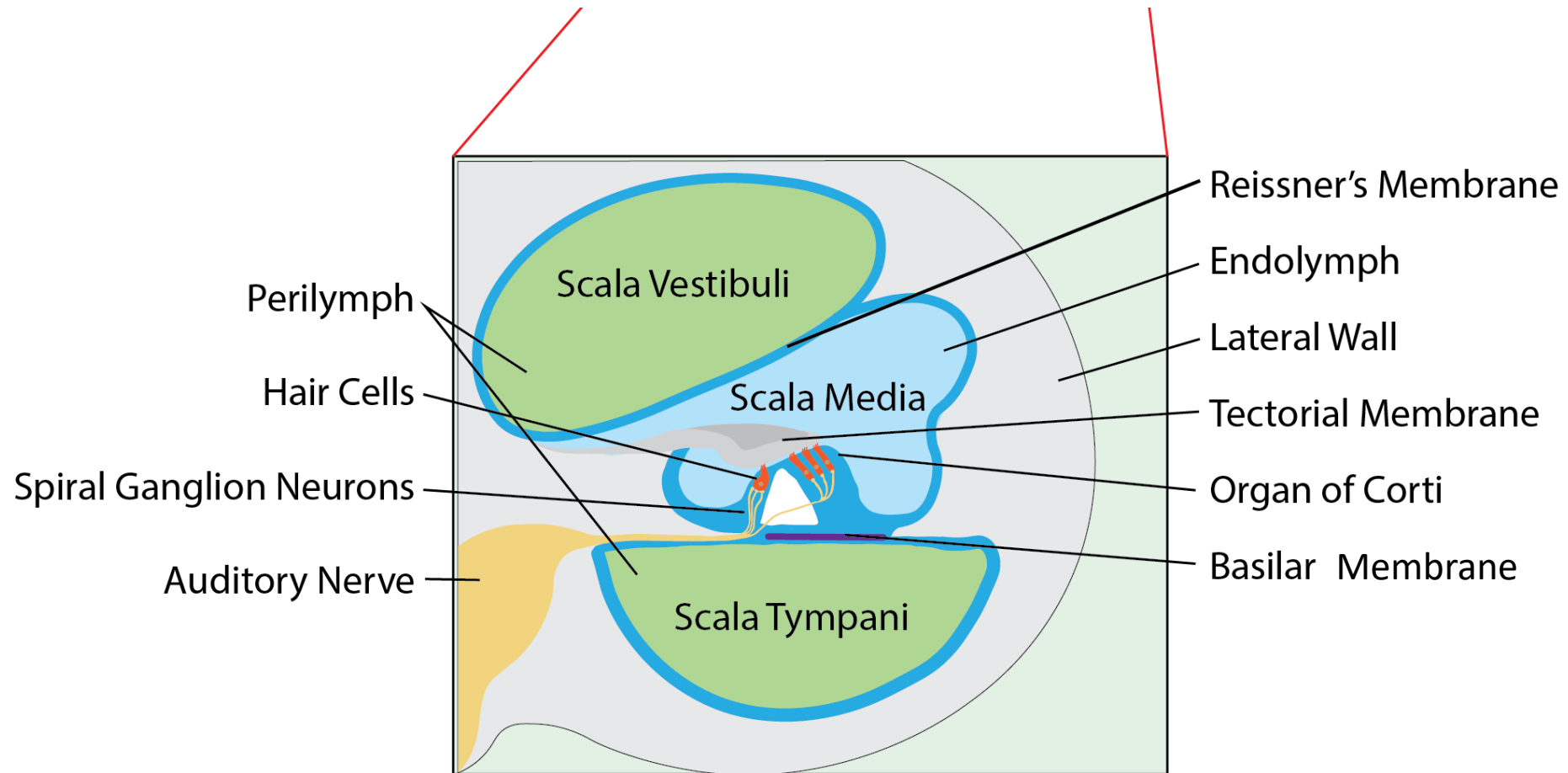


Norrie Disease Research Update

Contents:

Background on Hearing
Norrie Disease
Current Understanding
Current Research Findings
Future Directions





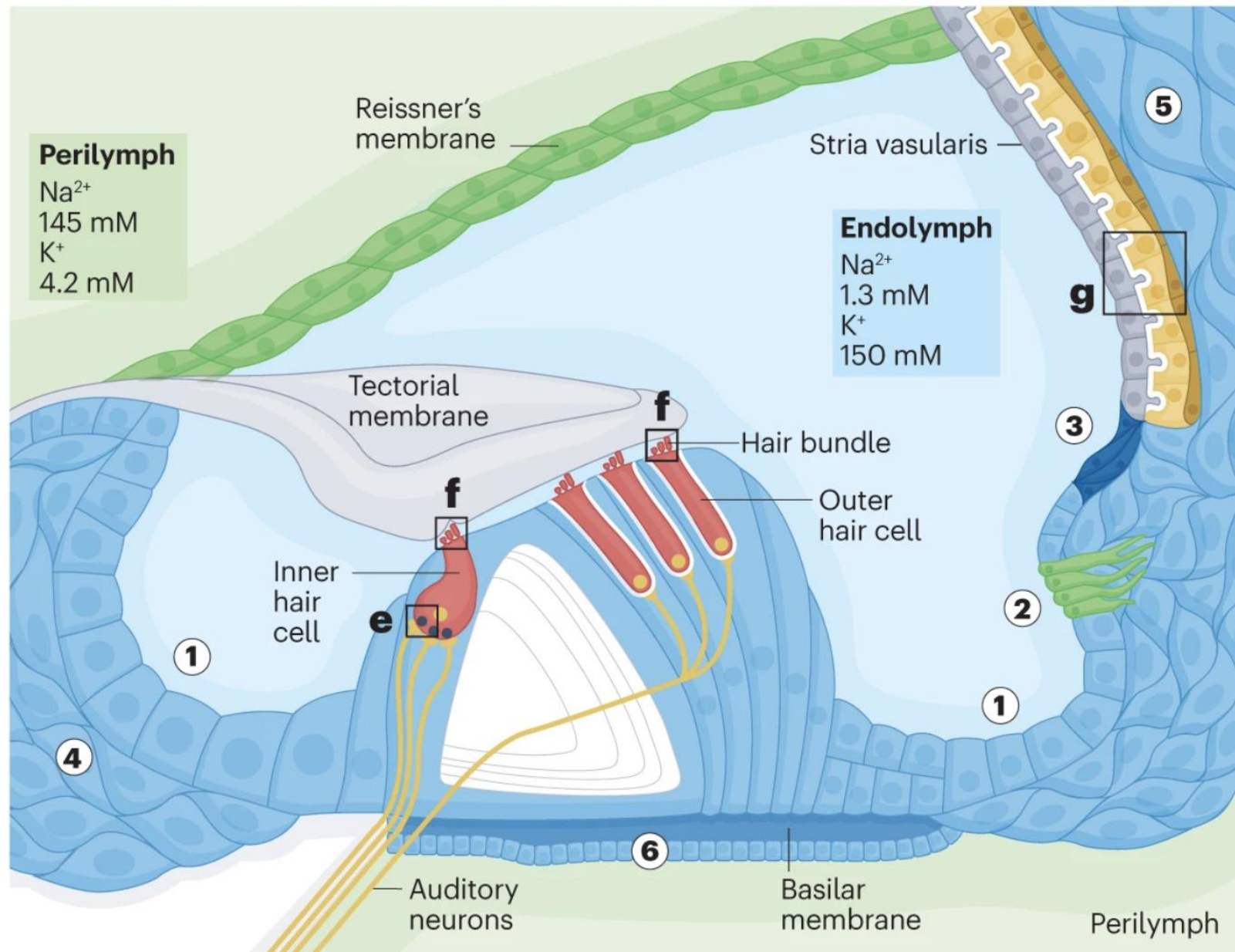
Introduction – the ear & hearing



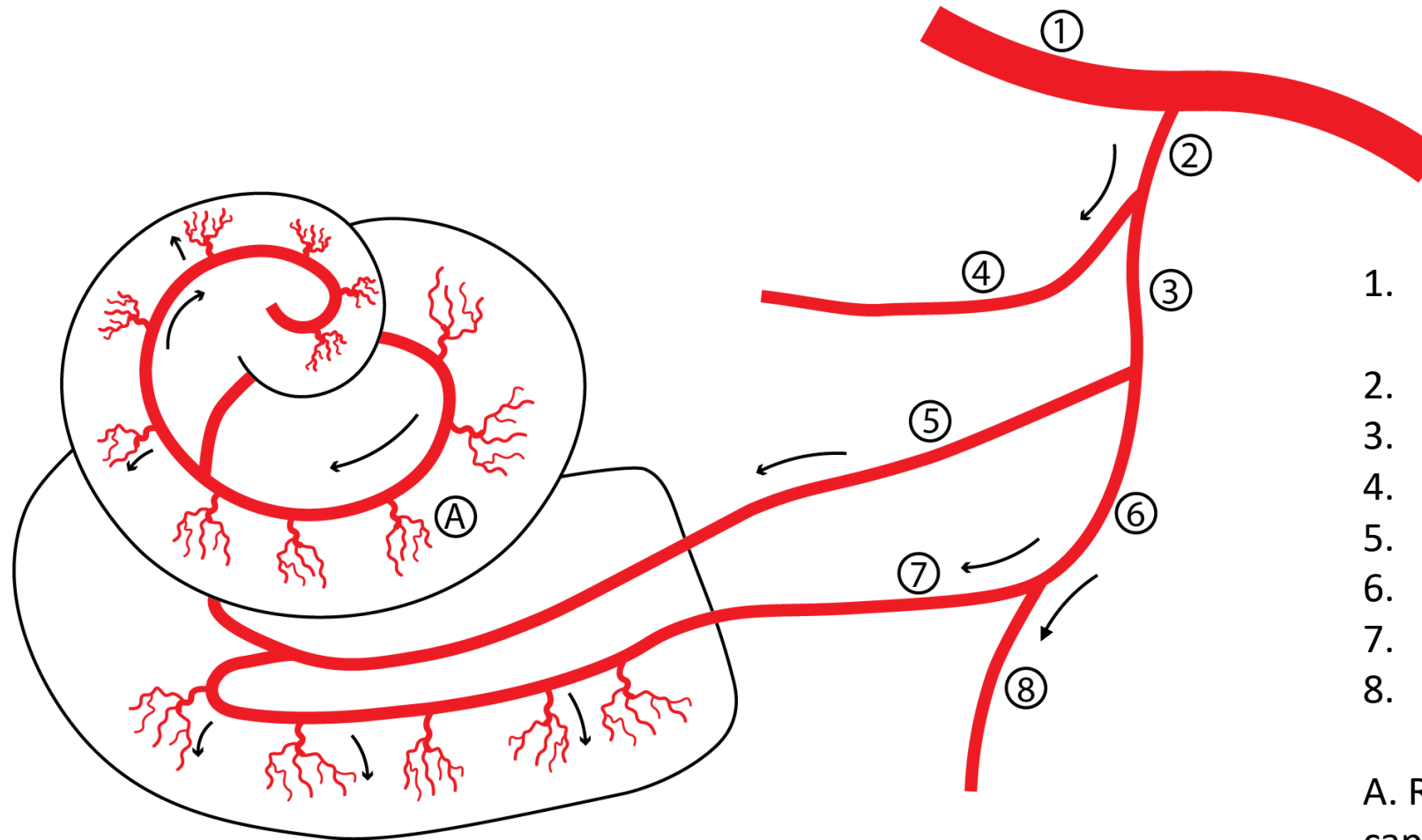
UCL



NIHR Great Ormond Street Hospital Biomedical Research Centre



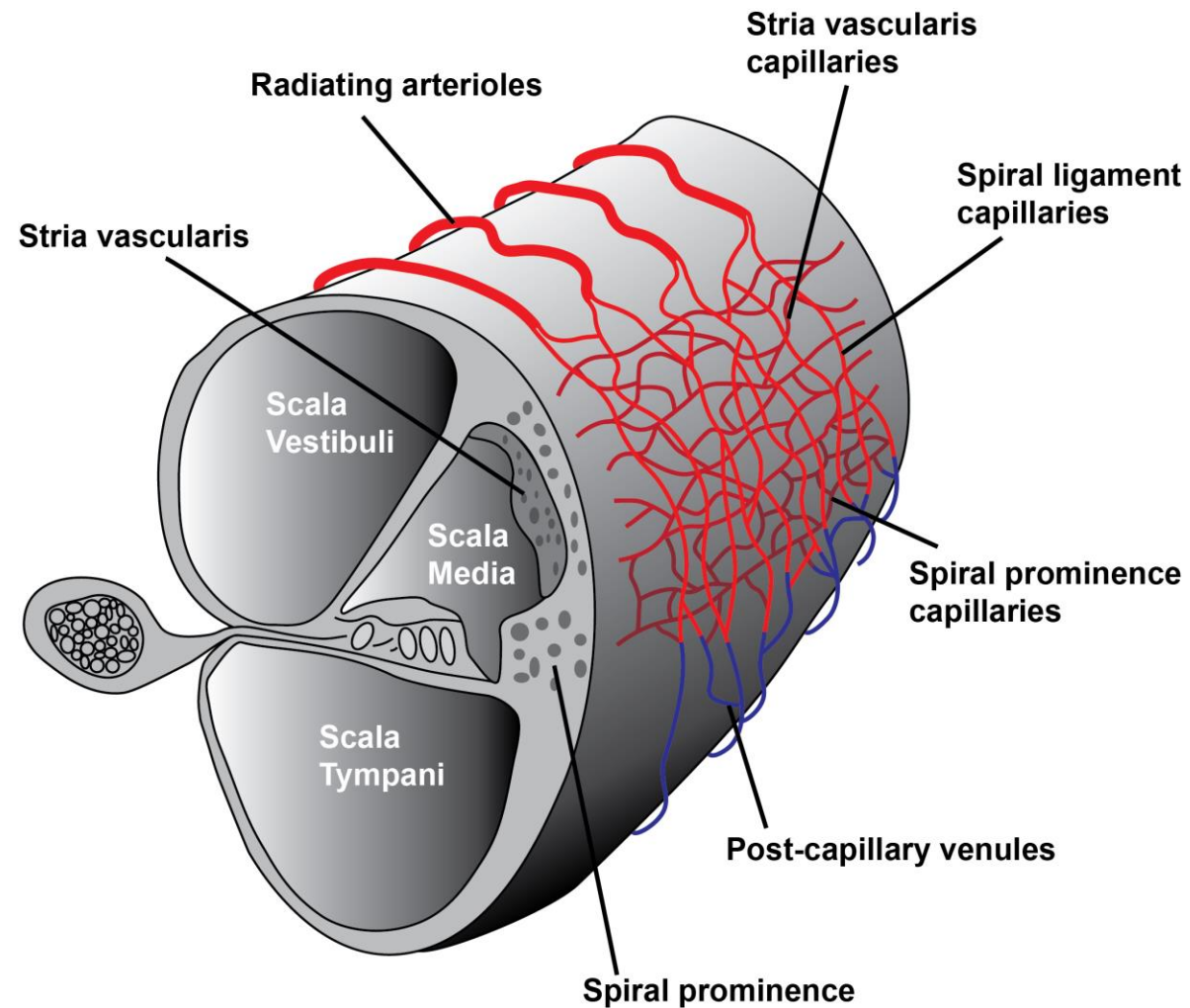
Petit, C., Bonnet, C. & Safieddine, S. Deafness: from genetic architecture to gene therapy. *Nat Rev Genet* 24, 665–686 (2023). <https://doi.org/10.1038/s41576-023-00597-7>

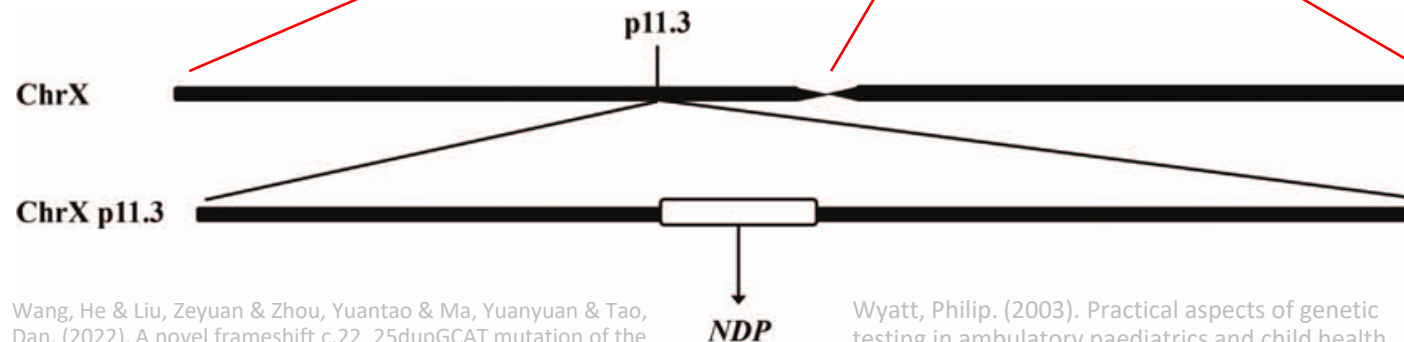


1. Anterior inferior cerebellar artery.
2. Labyrinthine artery.
3. Common cochlear artery.
4. Anterior vestibular artery.
5. Spiral modiolar artery.
6. Vestibulocochlear artery.
7. Cochlear branch.
8. Vestibular branch.

A. Radiating arterioles to supply the capillaries of the stria vascularis.

Arrows represent direction of blood flow.

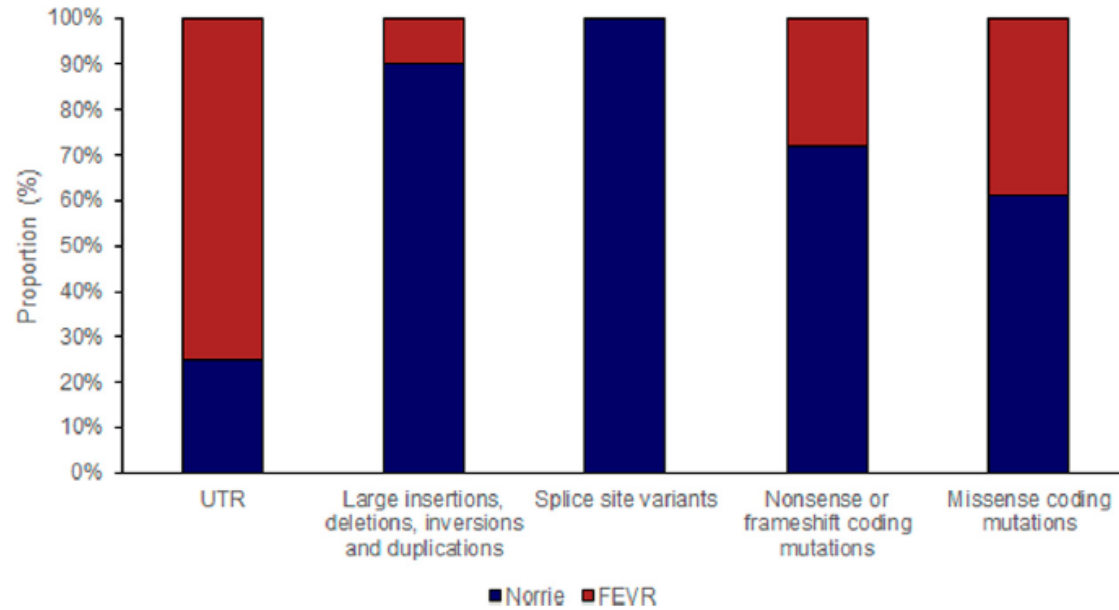




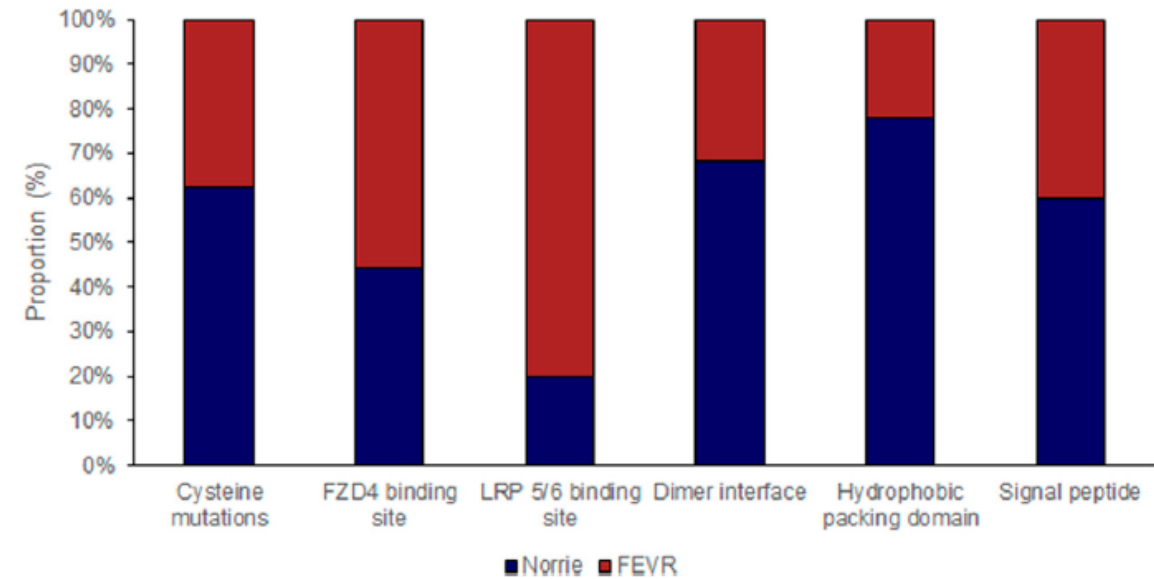
Wang, He & Liu, Zeyuan & Zhou, Yuantao & Ma, Yuanyuan & Tao, Dan. (2022). A novel frameshift c.22_25dupGCAT mutation of the NDP gene in a Chinese infant with Norrie disease: A case report. *Medicine*. 101. e28523.

Wyatt, Philip. (2003). Practical aspects of genetic testing in ambulatory paediatrics and child health care. *Paediatrics & child health*. 8. 20-3

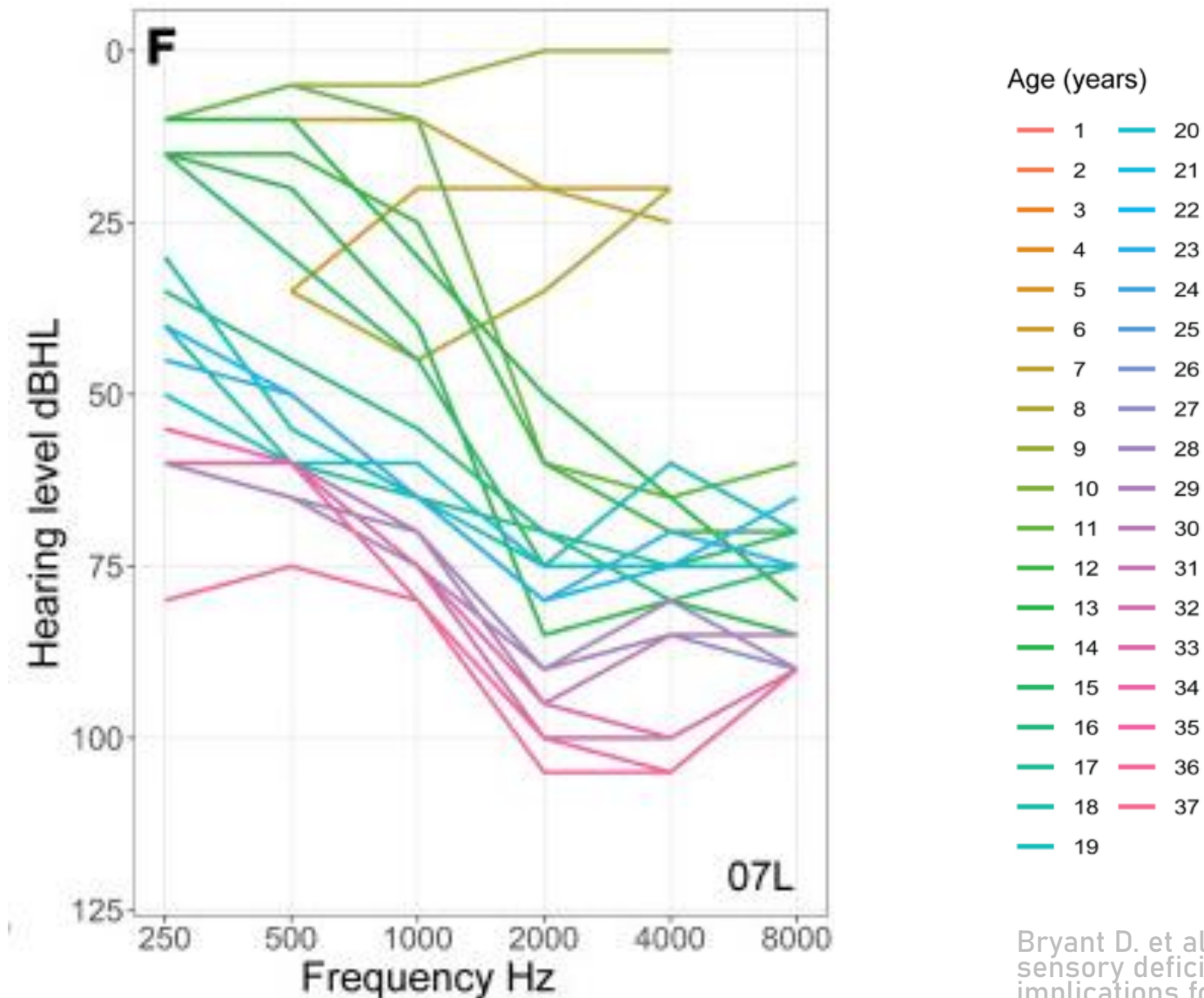
Mutation type VS Norrie or FEVR diagnosis



Domain of NDP cDNA affected by missense mutations VS Norrie or FEVR diagnosis



Norrie Disease

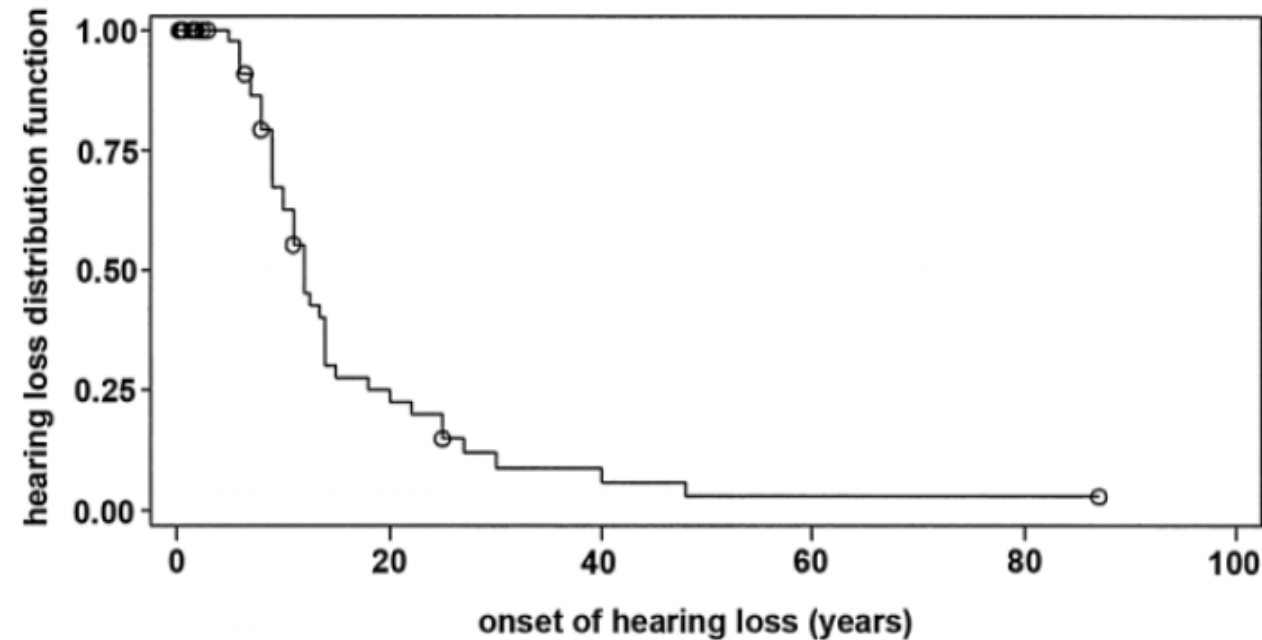
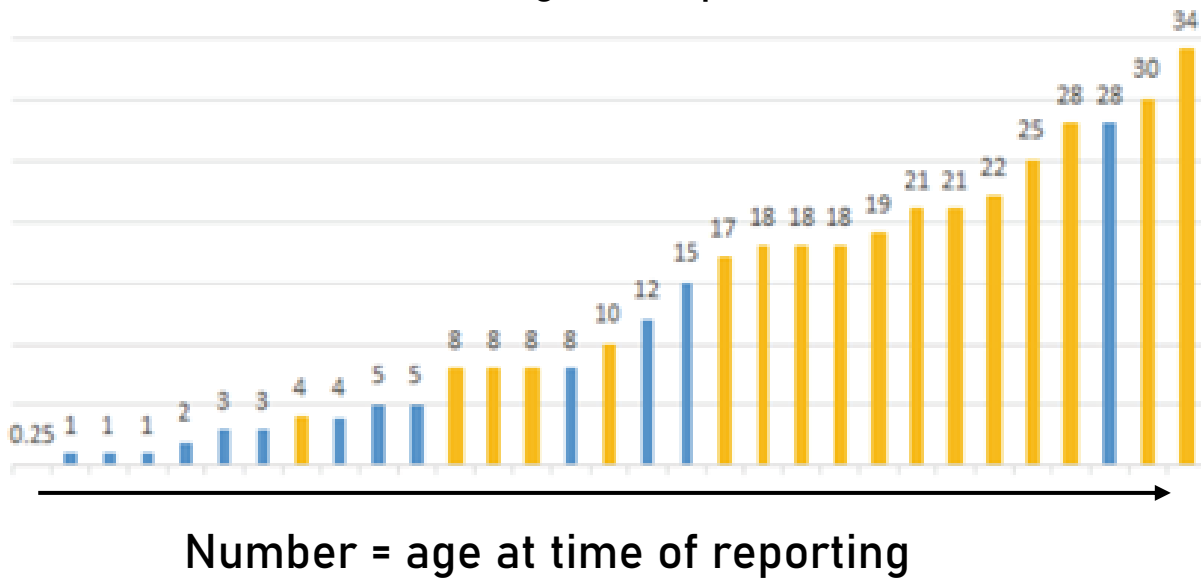


Bryant D. et al The timing of auditory sensory deficits in Norrie disease has implications for therapeutic intervention. *JCI Insight* 7;3 (2022)

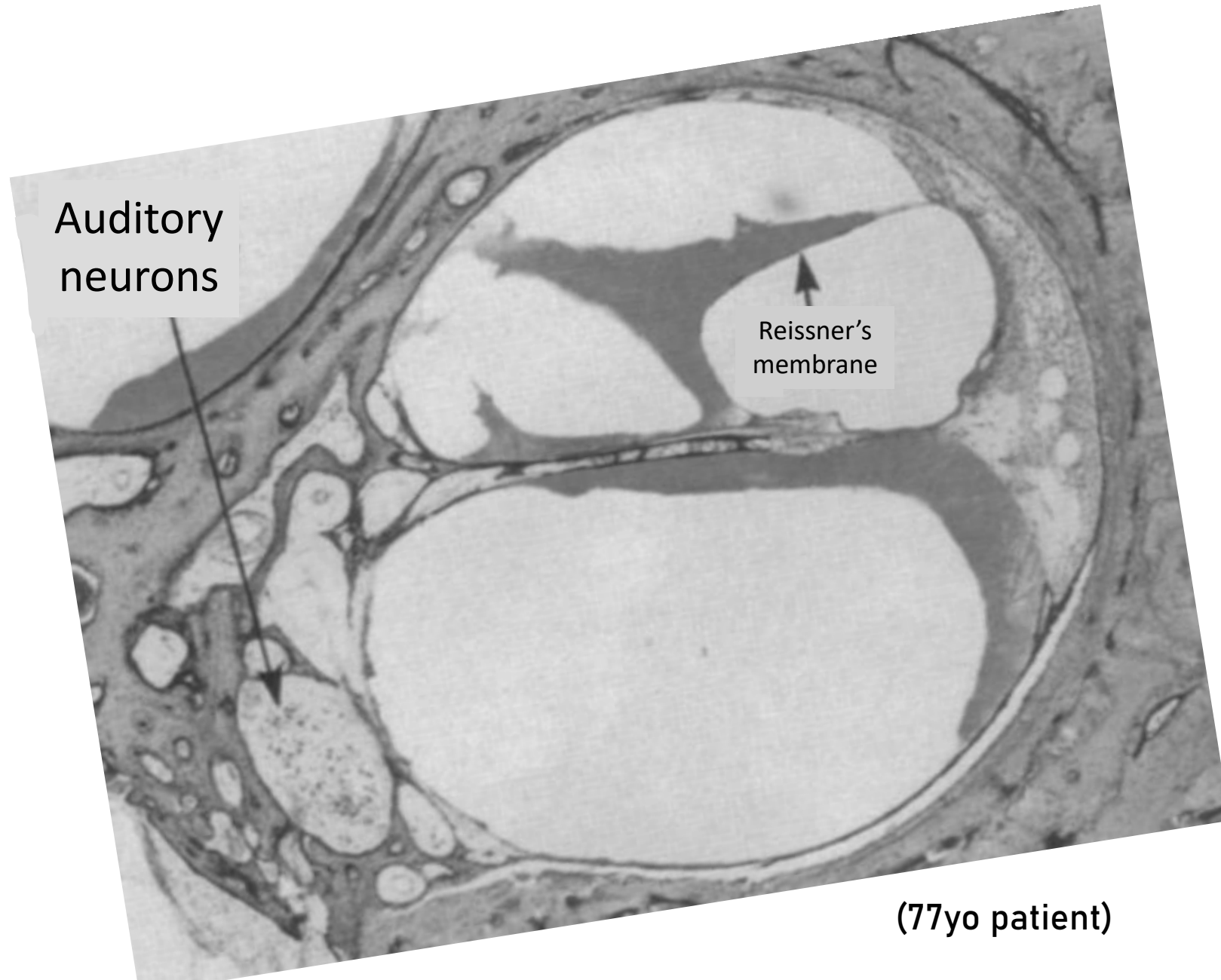
Survey of UK Norrie disease patients

Blue = no hearing loss reported

Yellow = hearing loss reported



Norrie Disease



(77yo patient)

Nadol JB Jr, Eavey RD, Liberfarb RM, Merchant SN, Williams R, Climenhager D, Albert DM. Histopathology of the ears, eyes, and brain in Norrie's disease (oculoacousticocerebral degeneration). Am J Otolaryngol. 1990 Mar-Apr;11(2):112-24



Ndp-KO

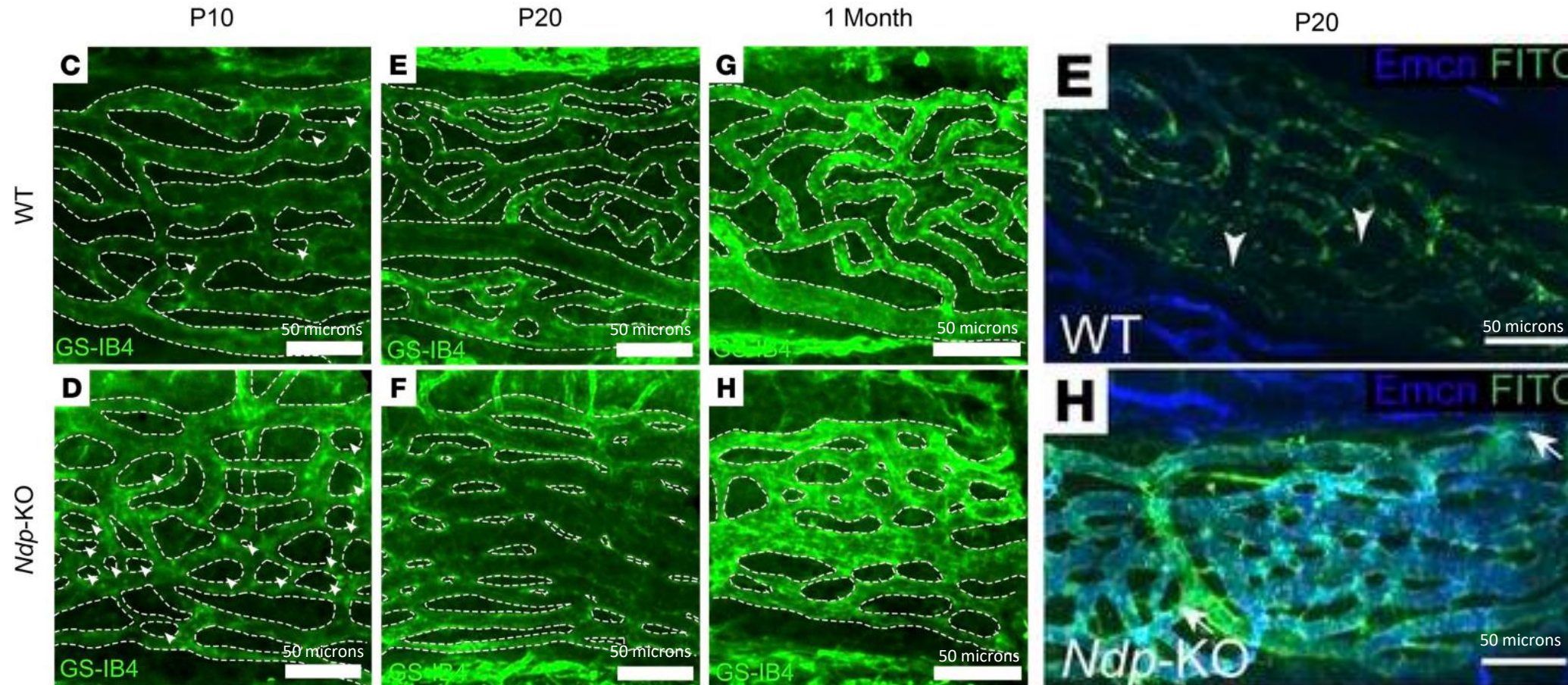
Norrie Disease -> abnormal blood vessels



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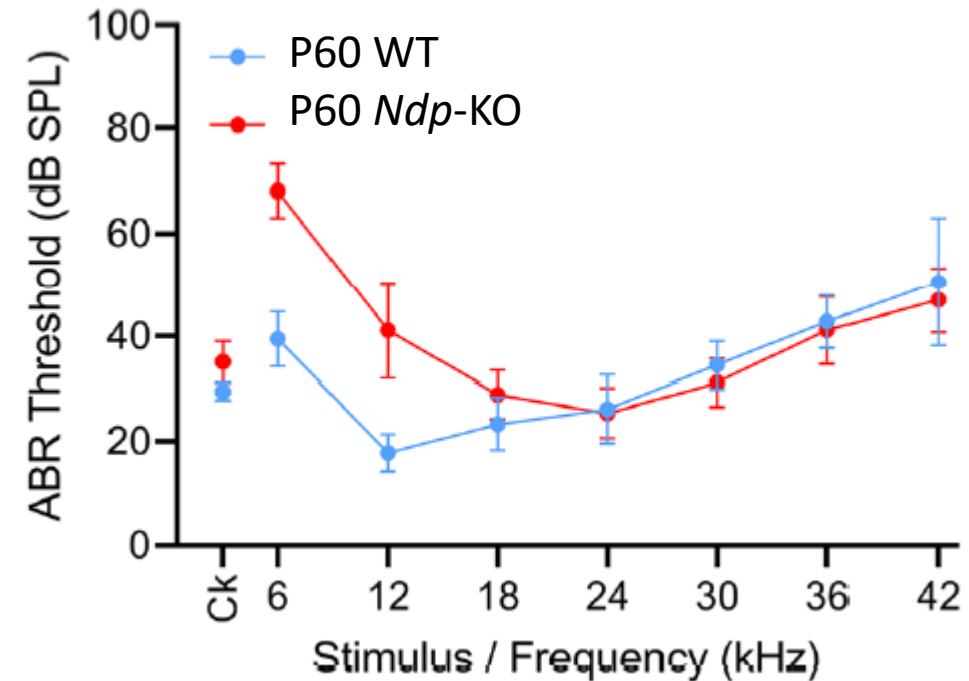
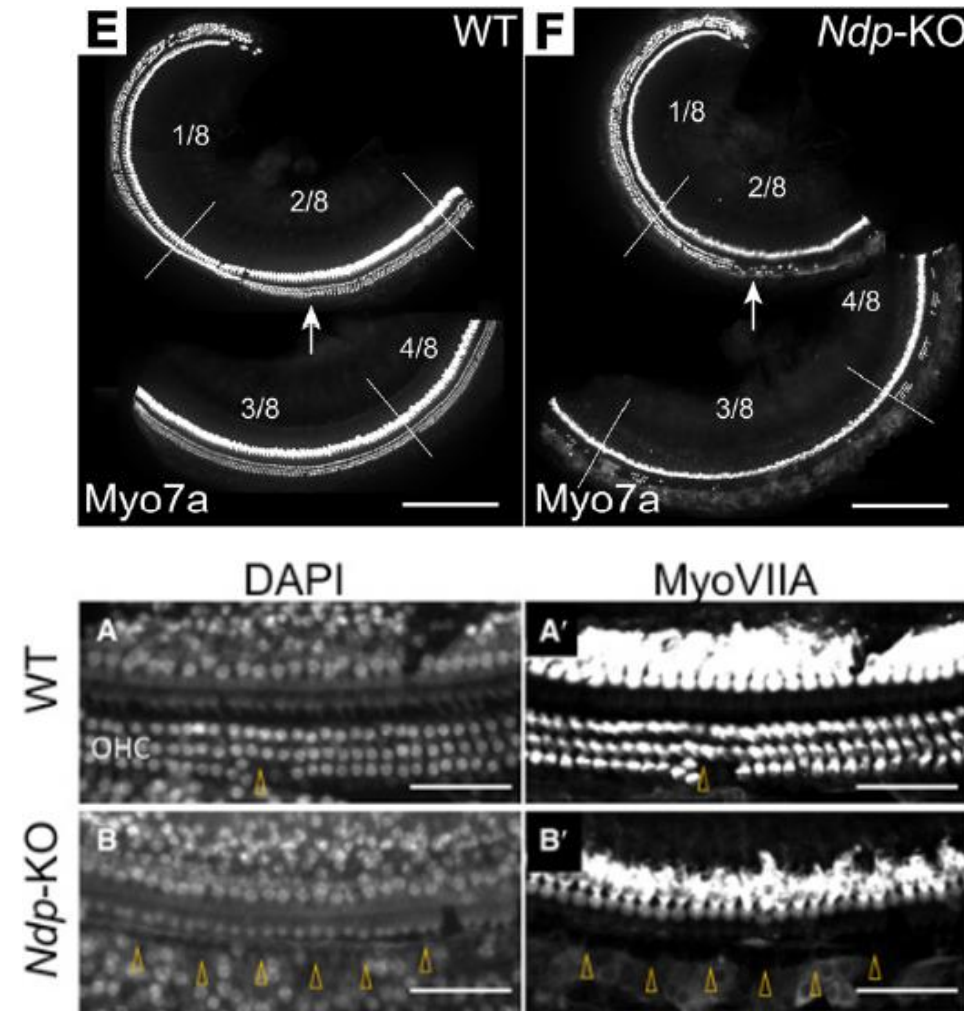


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Bryant D et al. Rescue of cochlear vascular pathology prevents sensory hair cell loss in Norrie disease. Proc Natl Acad Sci U S A. 2024 Dec 3;121(49):e2322124121. doi: 10.1073/pnas.2322124121

Norrie Disease -> in loss of hair cells+hearing



Bryant D et al. Rescue of cochlear vascular pathology prevents sensory hair cell loss in Norrie disease. *Proc Natl Acad Sci U S A*. 2024 Dec 3;121(49):e2322124121. doi: 10.1073/pnas.2322124121

Our virus

AAV9 capsid

Proof-of-concept construct:

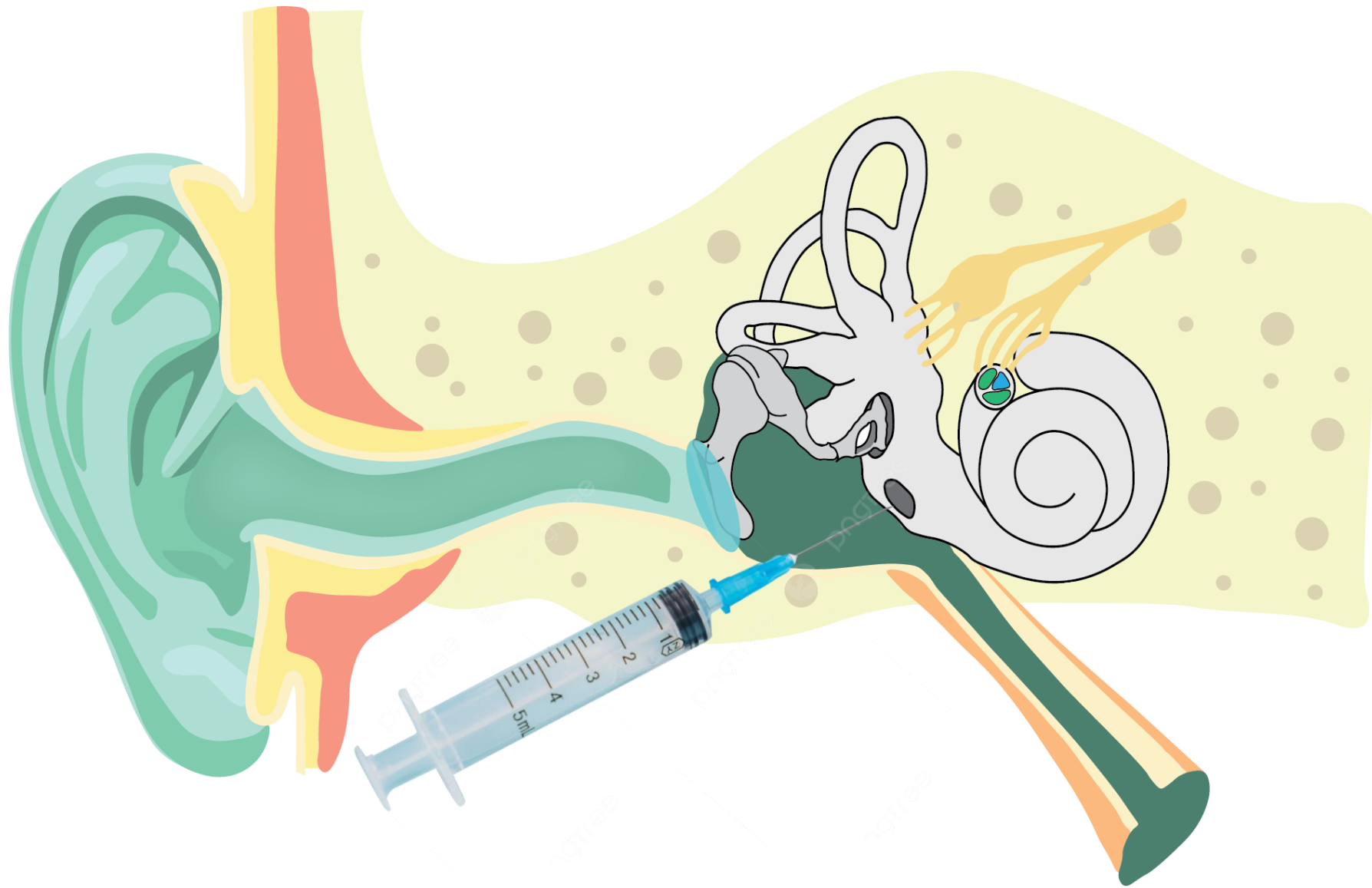


- Green fluorescent protein and flag tags included for monitoring the location of transduction
- Not appropriate for humans

Clinical construct:



- All tags removed
- Appropriate for humans



Proof-of-concept construct:

- Reaches the cochlea
- Preserves hair cells
- Preserves hearing
- Results will be published soon

(A research image was presented on this slide in the original meeting but has been removed for sharing)

Mechanism work

Established mechanism of blood vessel dysfunction that results in hair cell death and hearing loss

Further evidence for this is being worked on currently

Proof-of-concept work

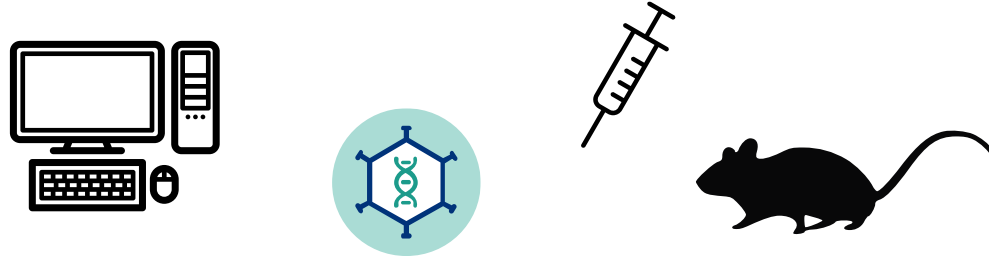
Good evidence for efficacy of our proof-of-concept gene therapy delivered directly into the inner ear

Findings will be synthesised into a publication

Pre-clinical development

Ongoing:
Requirement of evidence of efficacy of a clinically appropriate version of the gene therapy
Longer-term safety and toxicity studies

Proof-of-concept



Pre-Clinical Development

~several years

~£millions



Clinical Trials

> *Pharmaceut Med.* 2023 Sep;37(5):365-375. doi: 10.1007/s40290-023-00480-0. Epub 2023 Jun 7.

The Cost of Biotech Innovation: Exploring Research and Development Costs of Cell and Gene Therapies

Marco T Sabatini ¹, Mark Chalmers ²

Affiliations + expand

PMID: 37286928 DOI: 10.1007/s40290-023-00480-0

Clinical Trials

- 
- Phase 0: Checking action is as expected in small group of humans
 - Phase 1: Safety and dose optimisation in small group of humans
 - Phase 2: Safety and efficacy studies in larger group of humans
 - Phase 3: Efficacy vs pre-existing treatments
 - Phase 4: Long-term effects of treatment (on the market)

~10 years

Mechanism work

Further work to link vascular abnormalities to hair cell death and hearing loss, and establish underlying molecular mechanisms of this

Proof-of-concept work

New study to establish an *in vitro* model of Norrie disease from which we can gain insights into the disease, and in which we can test therapies

Pre-clinical development

Encouraging results from clinical version of gene therapy construct need to be finalised

Natural history study needs to be completed

PPIE group will be set up to guide ongoing research

- Critical for understanding disease progression
- &
- Critical to inform clinical trial design:
 - To demonstrate the clinical need
 - To assess who to give a new drug to first
 - To identify which clinical outcome measures are best for evaluating the efficacy of a new drug



Translations:

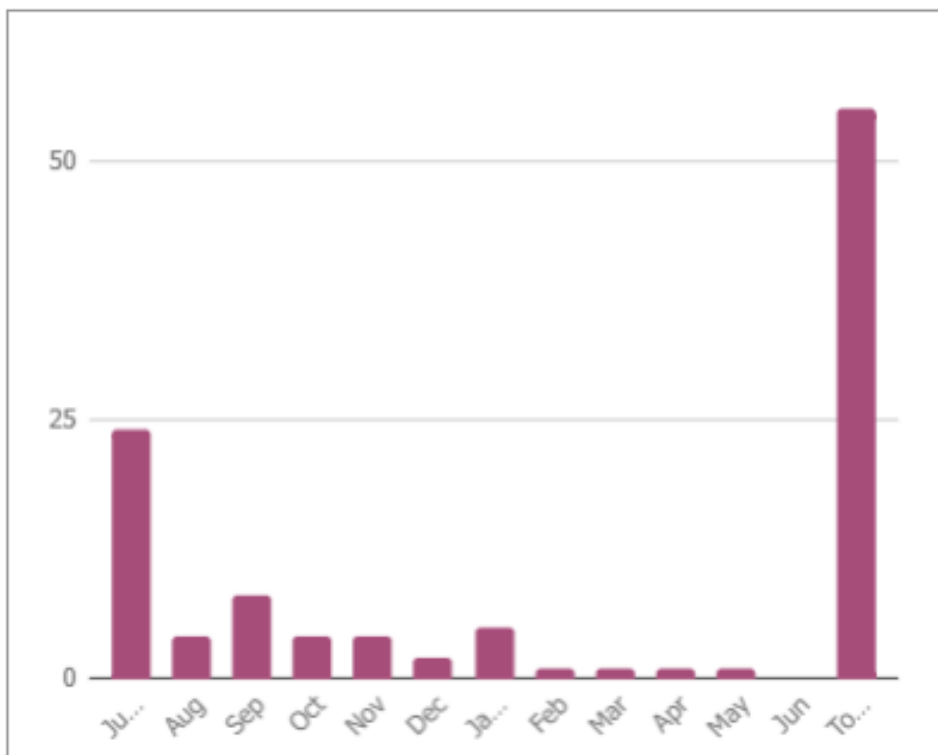
- English
- Spanish
- German
- French
- Arabic

Norrie Natural History Study

OVERVIEW

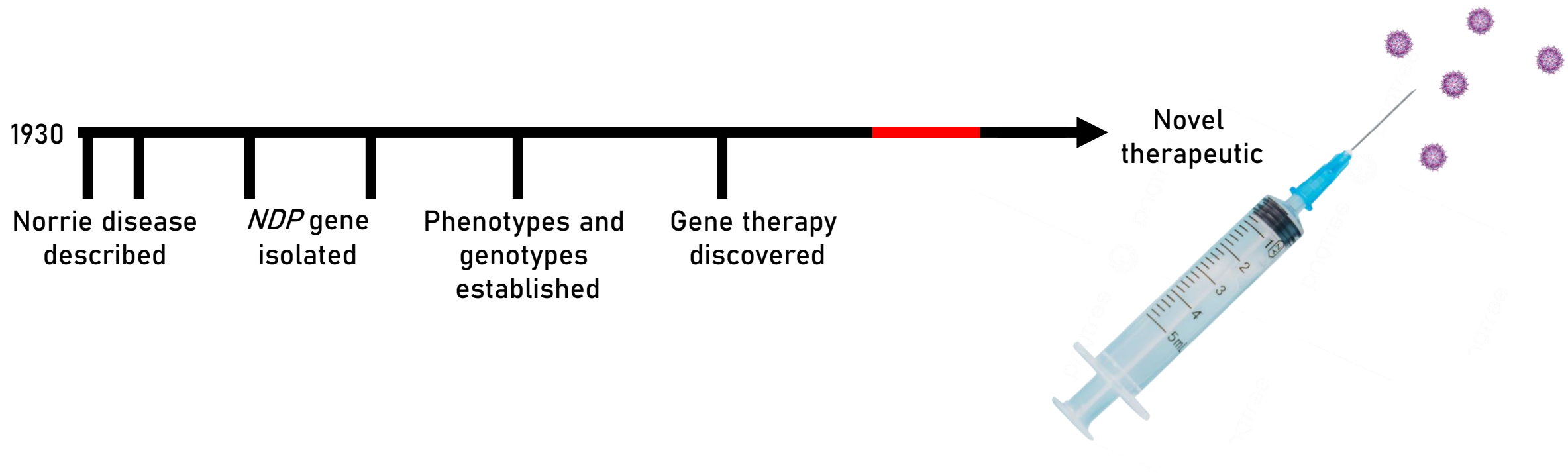
Participants

Monthly totals

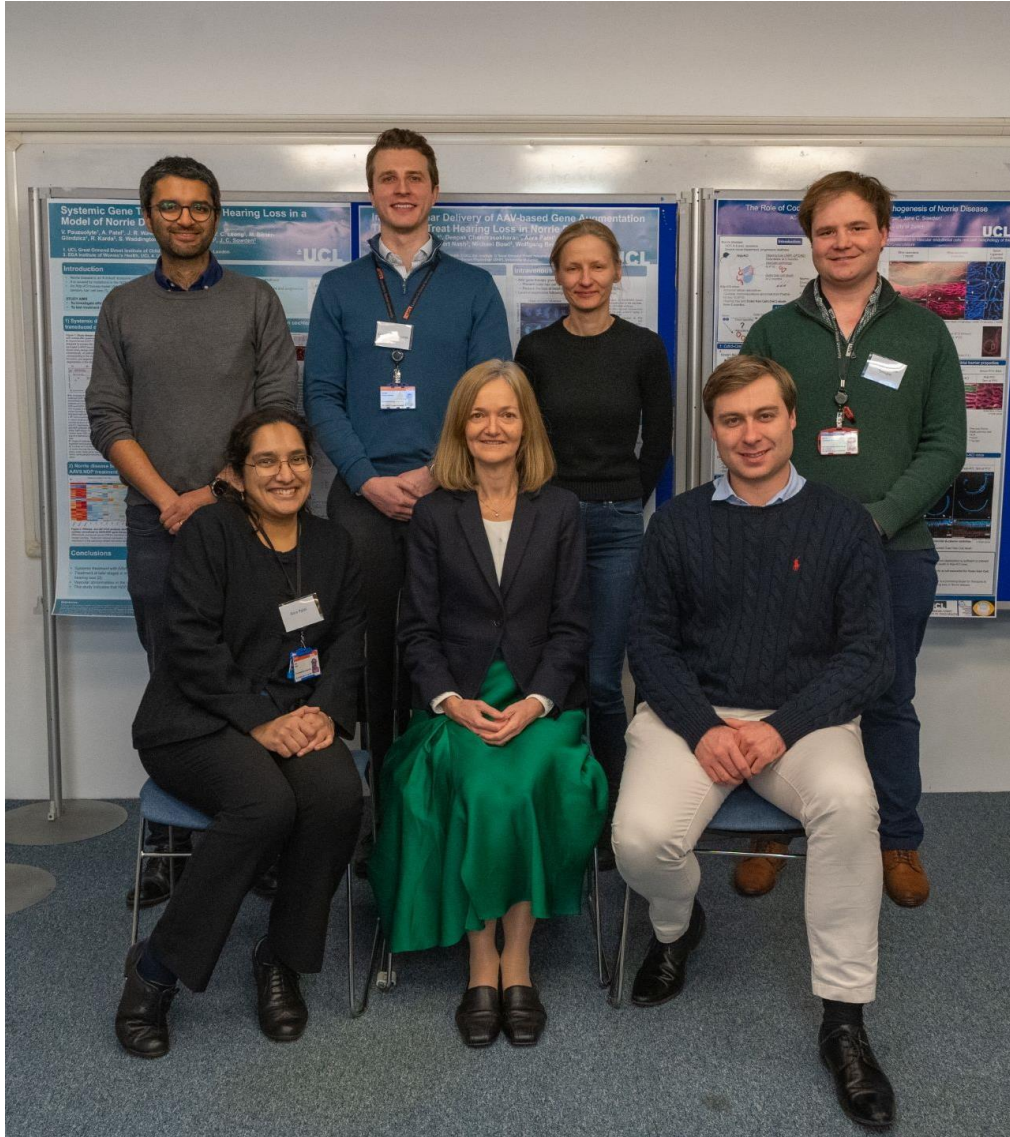


- 18 questionnaires previously completed
- 55 new questionnaires started
- 36 new questionnaires completed
- 17 genetic reports available
- 14 sets of audiology data available

Record ID	Norrie Disease Natural History Study	Consent	Child Participant Consent	16-18 Assent	Norrie Disease Id	Norrie Disease BG	Norrie Disease EYE	Norrie Disease GENE	Norrie Disease AUDIO	Norrie Disease DEV	Norrie Disease BEHAV	Norrie Disease NEURO	Norrie Disease SKELE	Norrie Disease VASC	Norrie Disease ENDO	Norrie Disease OTHER
21	☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22	☒	☐	☒	☐	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
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Thank you



GOS-ICH:

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Kyle O'Sullivan

Junge lab, Minnesota:

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Dr Lingling Zhang

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Mr Ollie Coombe-Tenant
Mr Deepak Chandrasekharan
Dr Valda Pauzuolyte
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