

Casting light on the genetics of age-related hearing loss: Insights from the Canadian Longitudinal Study on Aging



 @brittdrog



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WORLD REPORT *ON HEARING*



TODAY,

1

IN

5

PEOPLE
WORLDWIDE
LIVE WITH
HEARING LOSS

BY 2050,

1

IN

4

PEOPLE ARE
PROJECTED TO HAVE
PROBLEMS WITH
THEIR HEARING

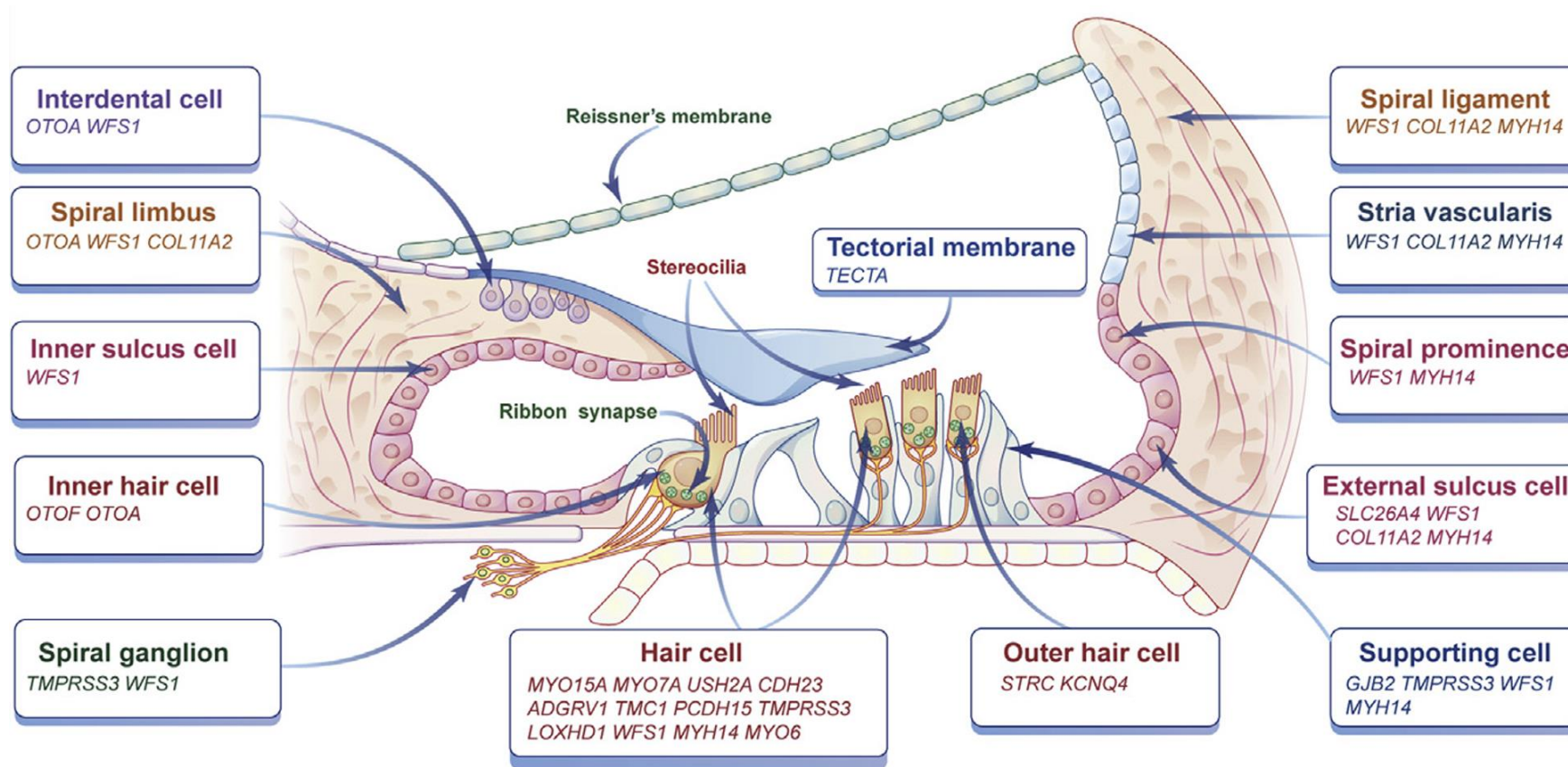
Hearing loss places a large burden on older adults

Most common sensory impairment in older people

~65% of Canadians >70 years experience hearing loss

↑ communication difficulties, social isolation, depression
& cognitive decline

Genetics plays an important role in hearing phenotypes



Jiang *et al.* *Mol Ther.* 2023;31:934-950.



The majority of hearing loss traits are polygenic

AAGCTA**T**TTGATATACACACATGTTGGGGTATA**C**CACACATAGGAGAGGAGATT**G**
ATTCCATTGACATTACAGTTACAGATATATATACAGGATAATAAAGCTATTTGATAT
ACACACATGTTGGGGTATACACACATAGGAGAGGAGATTGATTCCATTGACATTAC
AGTTACT**T**AGATATATATACAGGATAATAAA**A**GCTATTTGATA**G**TACACACA**A**ATGTT
GGGGTATACACACATAGGAGAGGAGATTGATTCCATTGACATTACAGTTACAC**C**GA
TATATAT**T**ACAGGATAATATAAGCTATTTGATATACACACATGTTGGGGTATACACA
CATA**A**GGAGAGGAGATTGATTCCATTGACATTACAGTTACAGAT**G**ATATATACAGG
GATACATATAAGCTATTTGATATACACACATGTTGGGGTATACACACATAGGAGAG
GAGATTGATTCCATTGACATTACAGTTACAGATATATATACAGGATAATATAAGCT**T**
ATTTGATATACA**C**CACATGTTGGGGTATACACACATAGGAGAGGAGATTGATTCCA
TTGA**C**CATTACAGTTACAGATATATATACAGGATA**A**CATAAAGCTATTTGATATACAC
ACATGTTGGG**C**GTATACACACATAGGAGAGGAGATTGATTCCATTGACATTACAGT

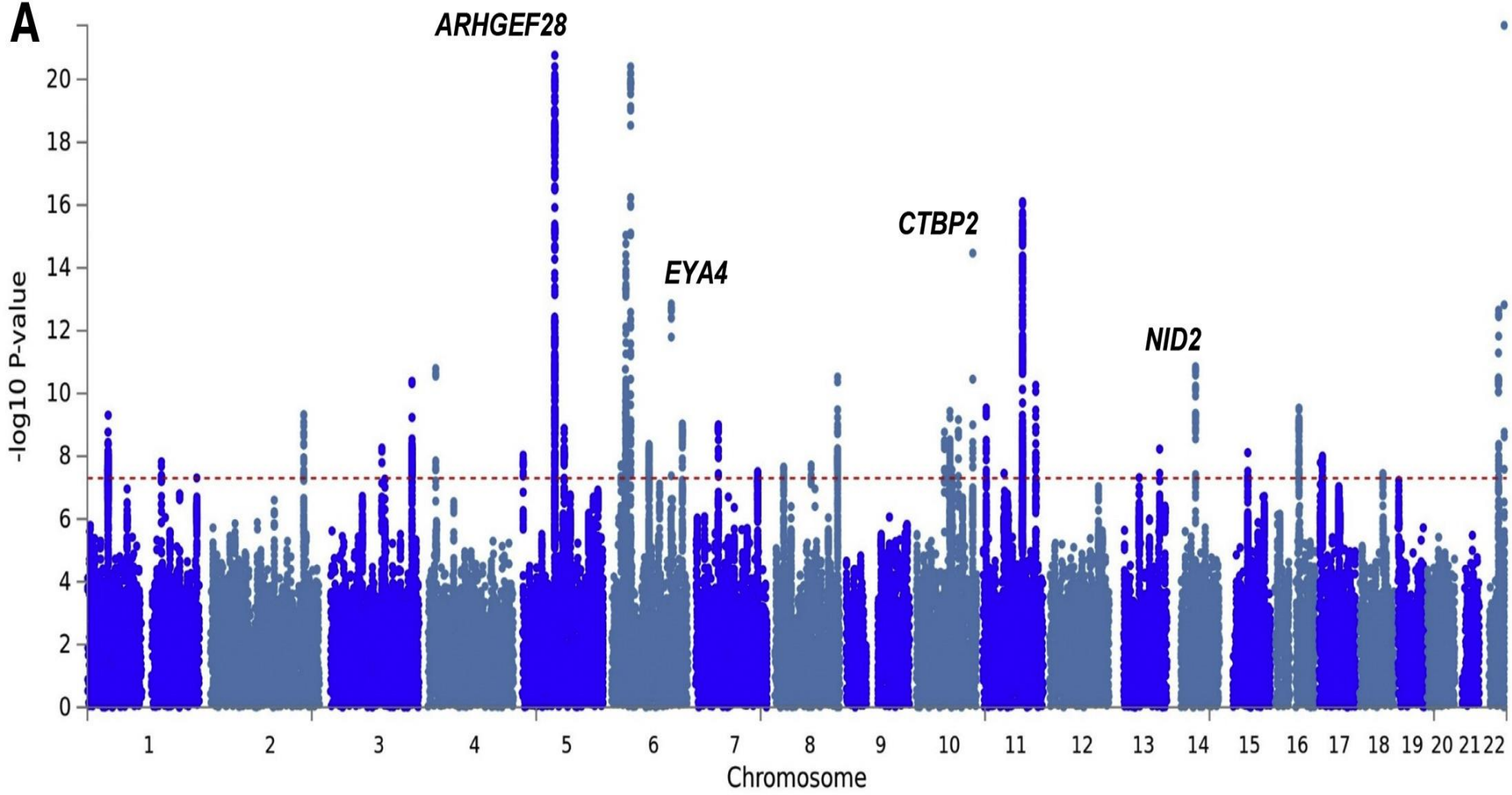


How do we **identify** genetic variants contributing to **hearing loss**?

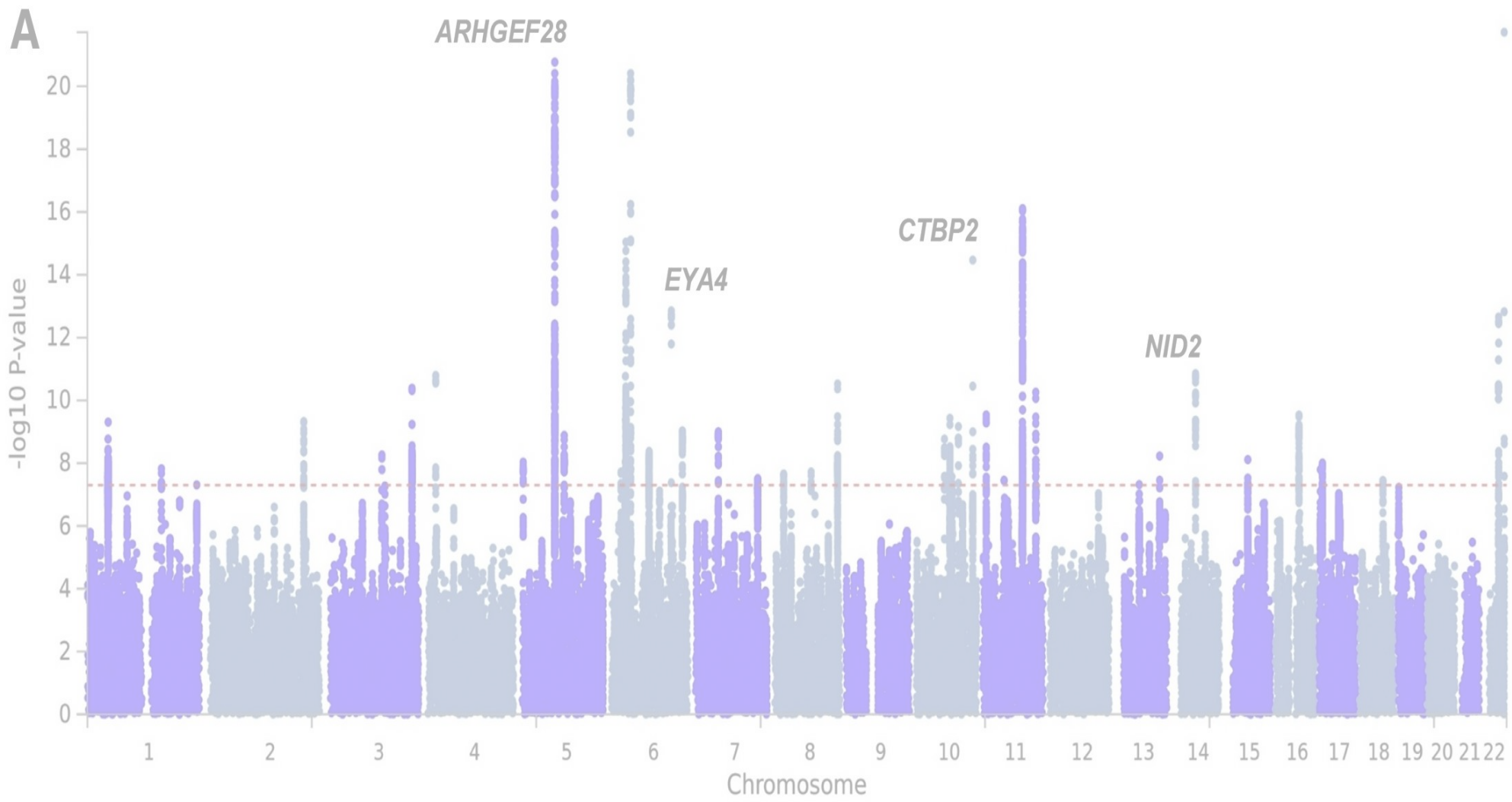
AAGCTA**T**TTGATATACACACATGTTGGGGTATA**C**CACACATAGGAGAGGAGATT**G**
ATTCCATTGACATTACAGTTACAGATATATATACAGGATAATAAAGCTATTTGATAT
ACACACATGTTGGGGTATACACACATAGGAGAGGAGATTGATTCCATTGACATTAC
AGTTACT**T**AGATATATATACAGGATAATAAA**A**GCTATTTGATA**G**TACACACA**A**ATGTT
GGGGTATACACACATAGGAGAGGAGATTGATTCCATTGACATTACAGTTACAC**C**GA
TATATAT**T**ACAGGATAATATAAGCTATTTGATATACACACATGTTGGGGTATACACA
CATA**A**GGAGAGGAGATTGATTCCATTGACATTACAGTTACAGAT**G**ATATATACAGG
GATACATATAAGCTATTTGATATACACACATGTTGGGGTATACACACATAGGAGAG
GAGATTGATTCCATTGACATTACAGTTACAGATATATATACAGGATAATATAAGCT**T**
ATTTGATATACA**C**CACATGTTGGGGTATACACACATAGGAGAGGAGATTGATTCCA
TTGA**C**CATTACAGTTACAGATATATATACAGGATA**A**CATAAAGCTATTTGATATACAC
ACATGTTGGG**C**GTATACACACATAGGAGAGGAGATTGATTCCATTGACATTACAGT

Large-scale **genome-wide association studies** (GWAS) can identify genetic variants associated with **hearing loss**

GWAS identifies 44 independent associated genomic loci for self-reported adult hearing difficulty in UK Biobank

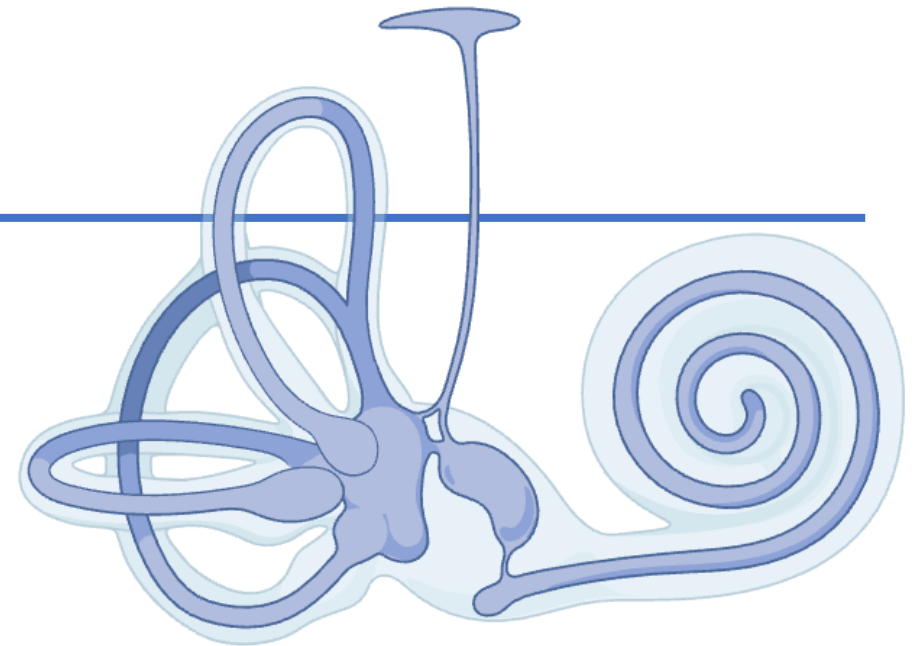


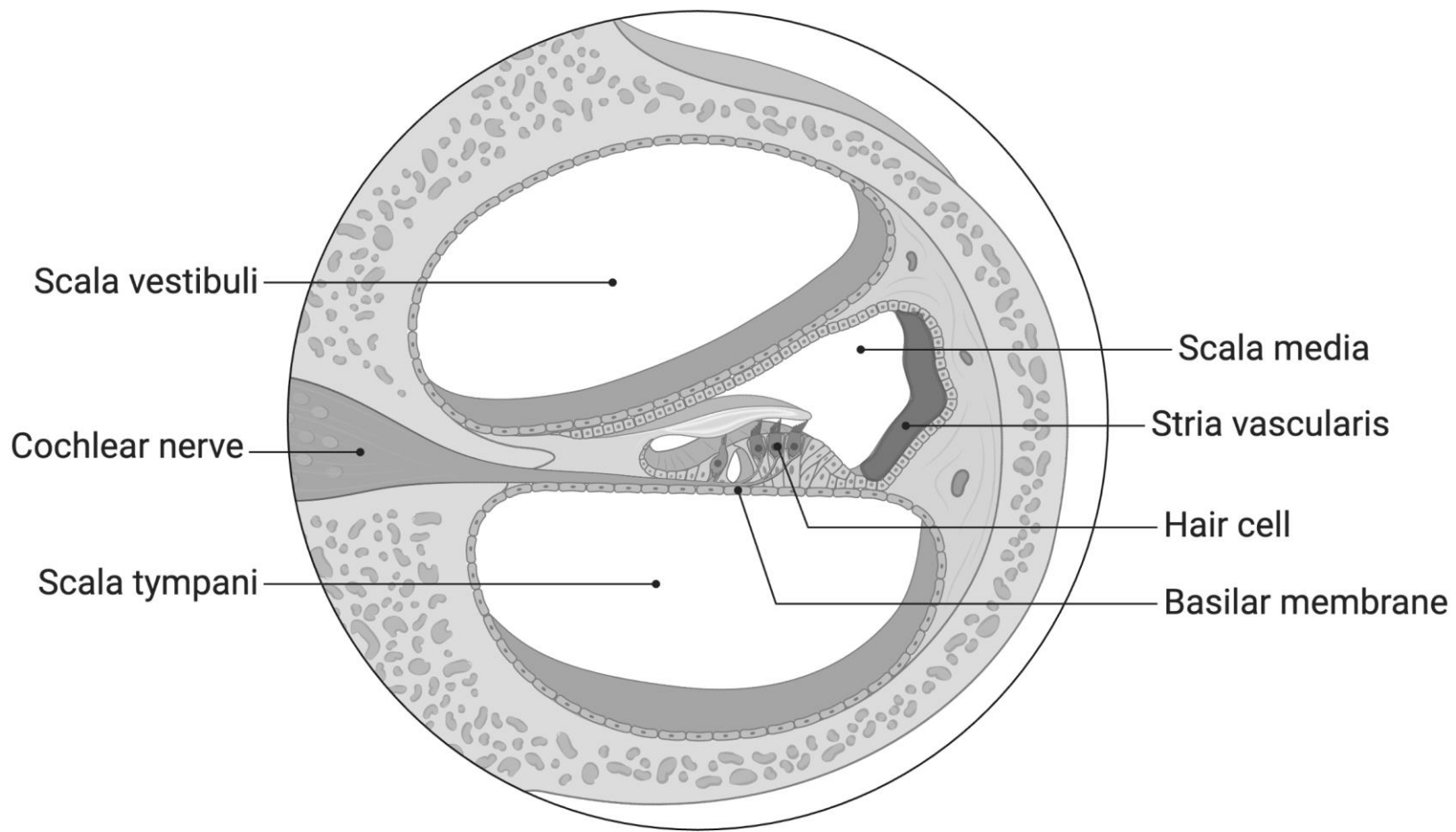
GWAS identifies 44 independent associated genomic loci for self-reported adult hearing difficulty in UK Biobank



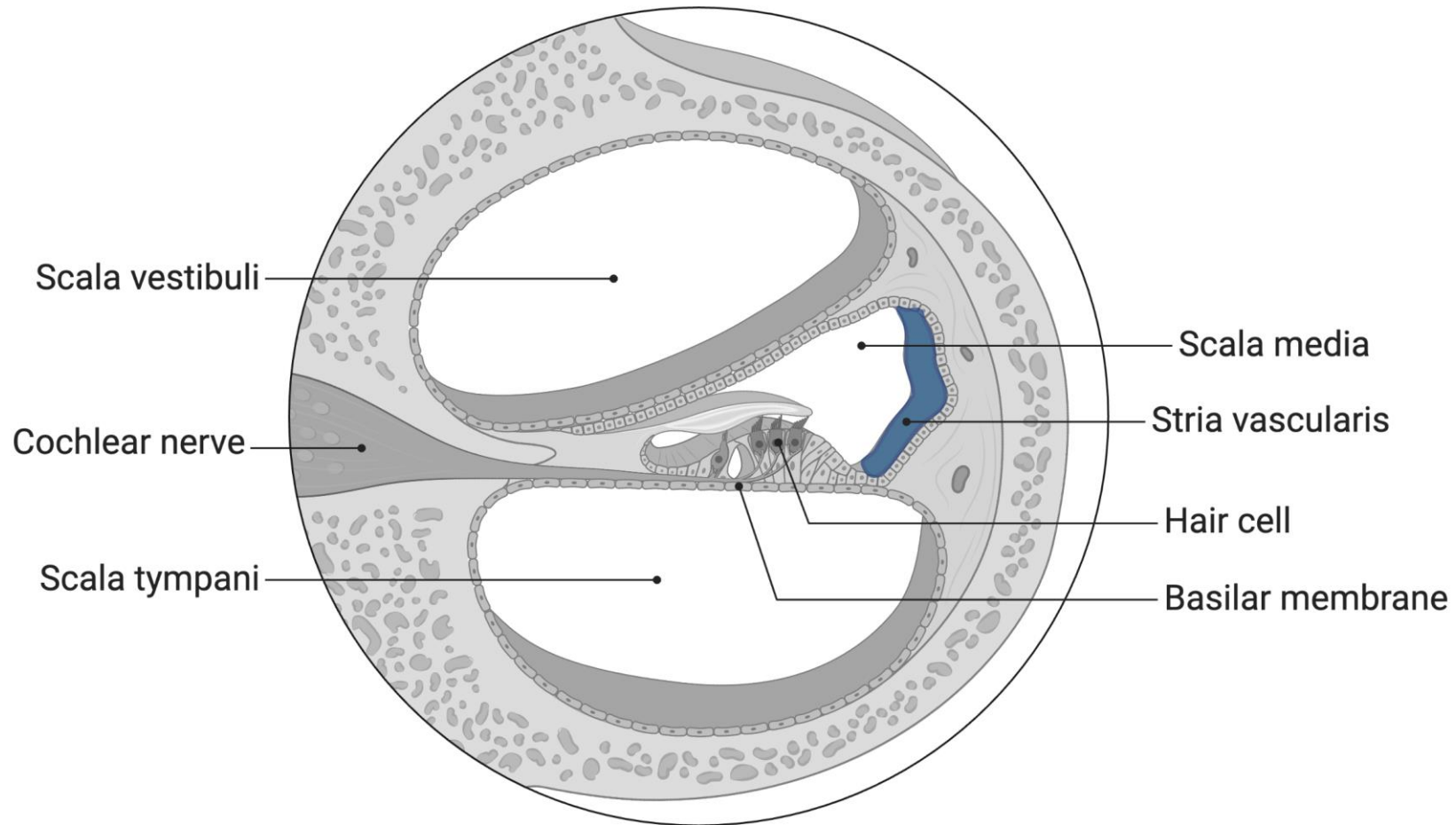
Knowledge gap: No large-scale investigation of genetic variants that contribute to **specific hearing phenotypes**

Diverse pathologies implicated in different hearing phenotypes

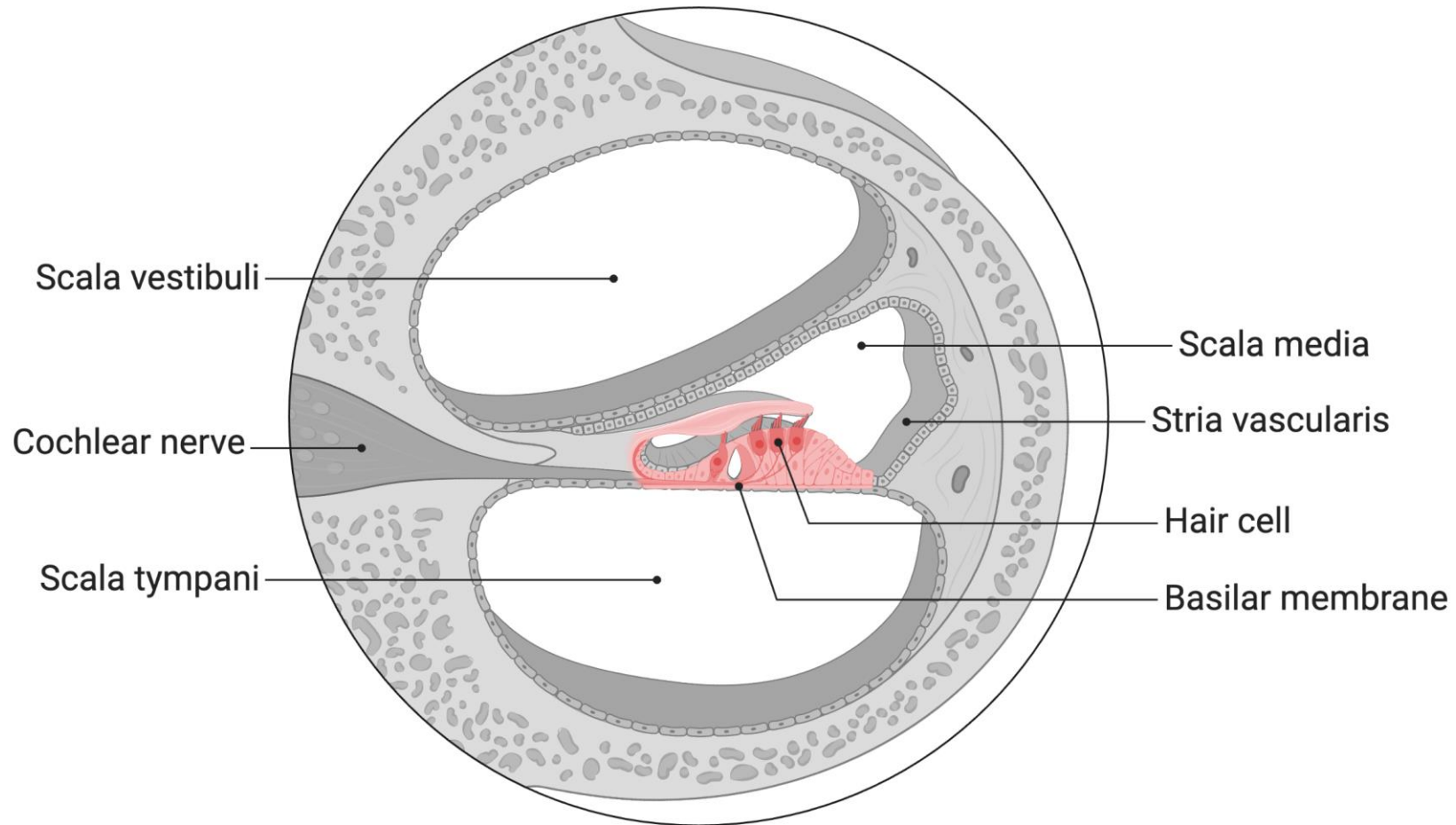




Hearing loss due to age-related sensorineural degeneration

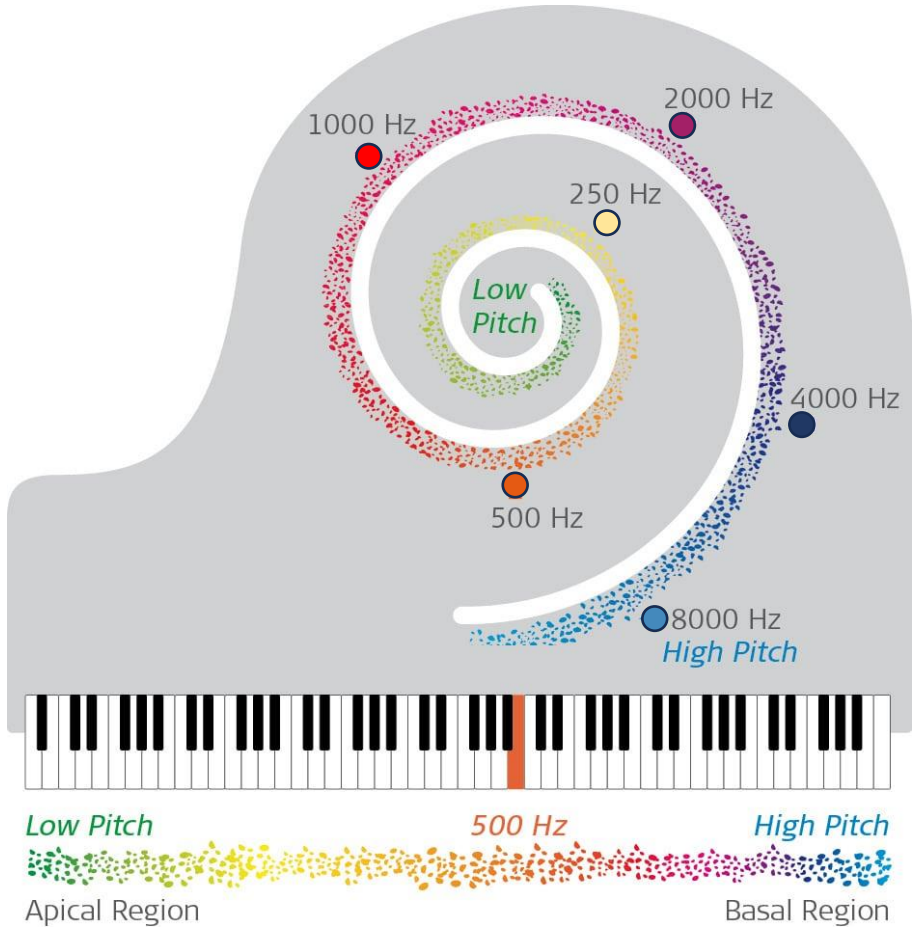
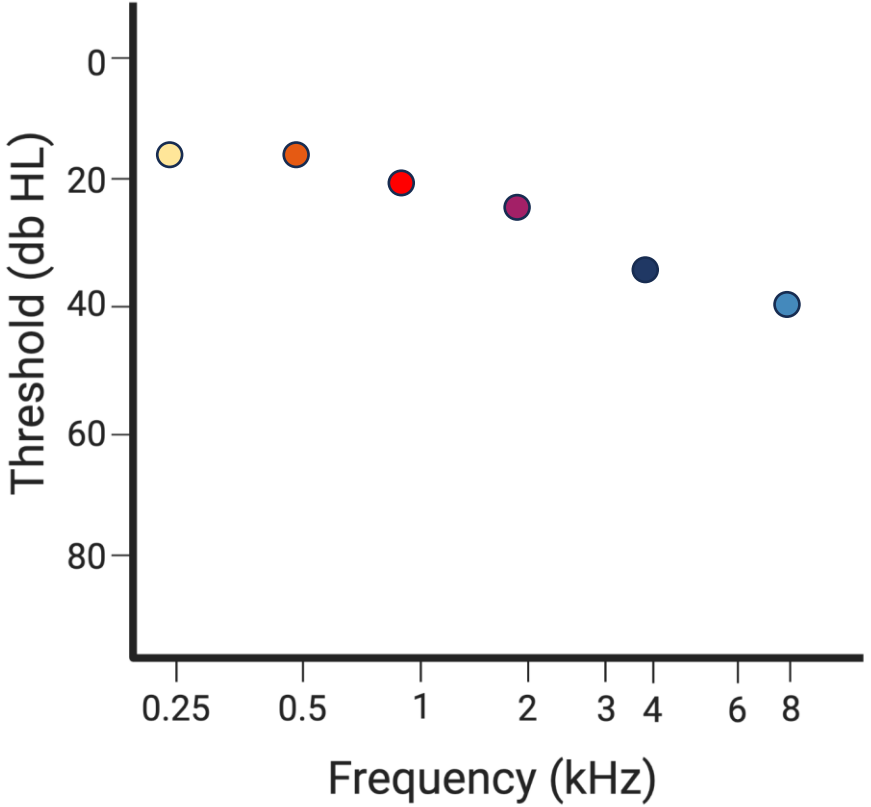


Hearing loss due to noise exposure

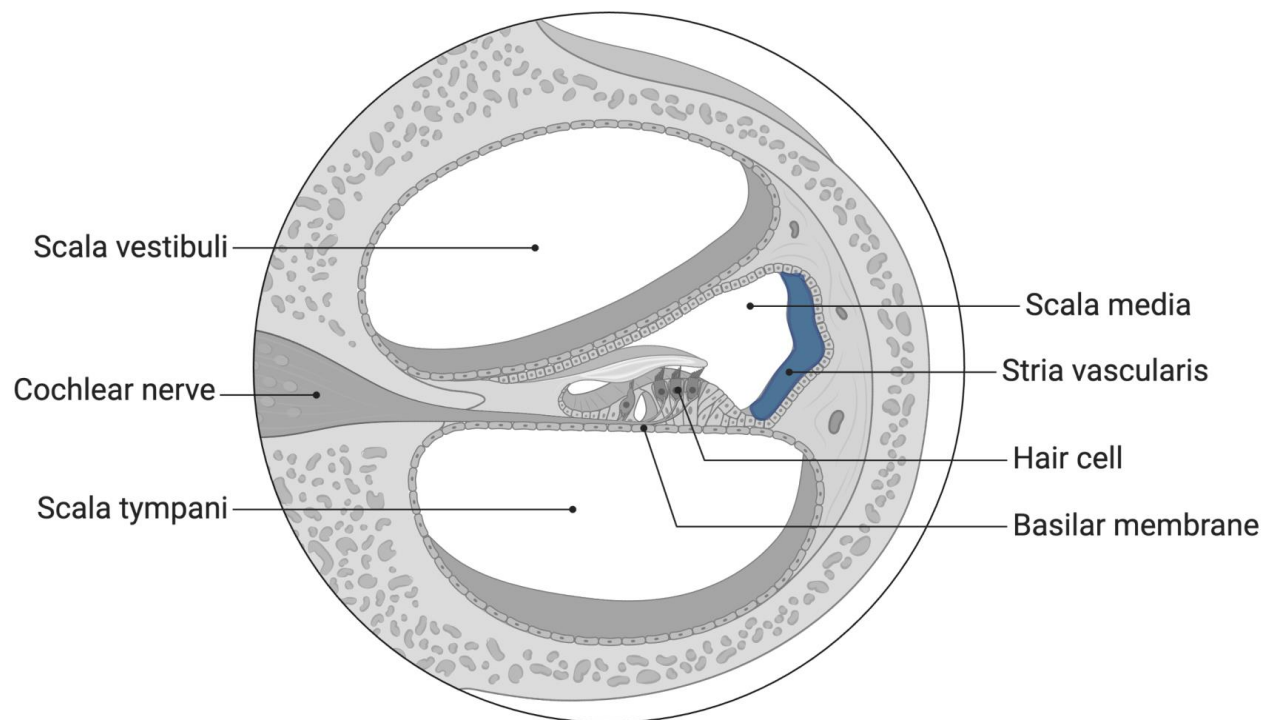
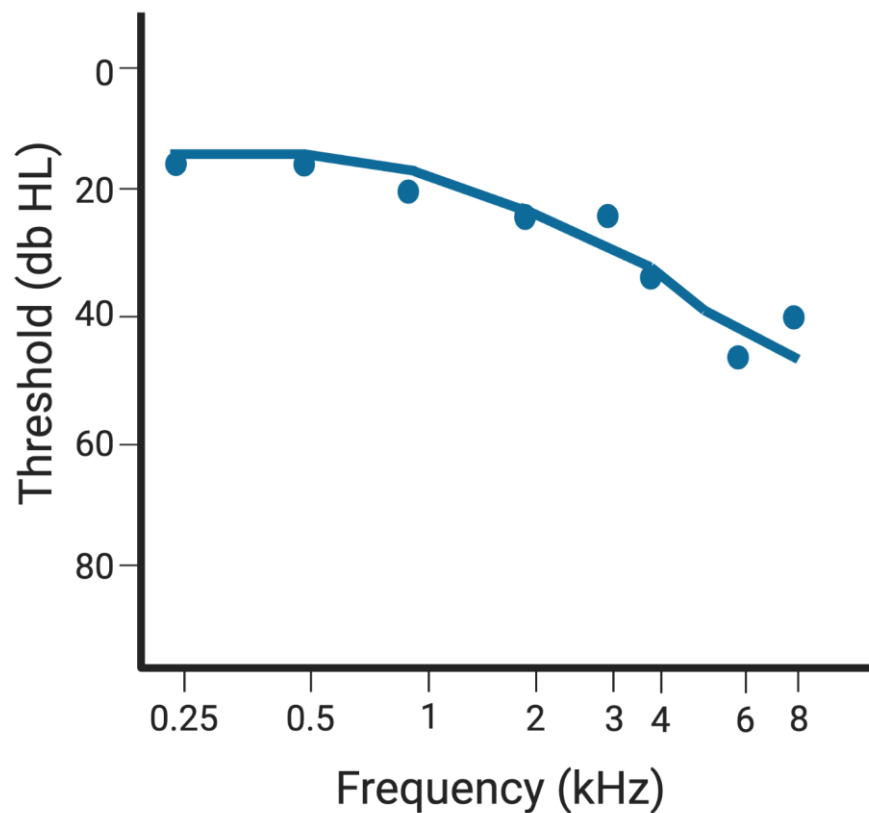


~~Self-report~~ Audiograms provide a tool to more carefully phenotype hearing loss

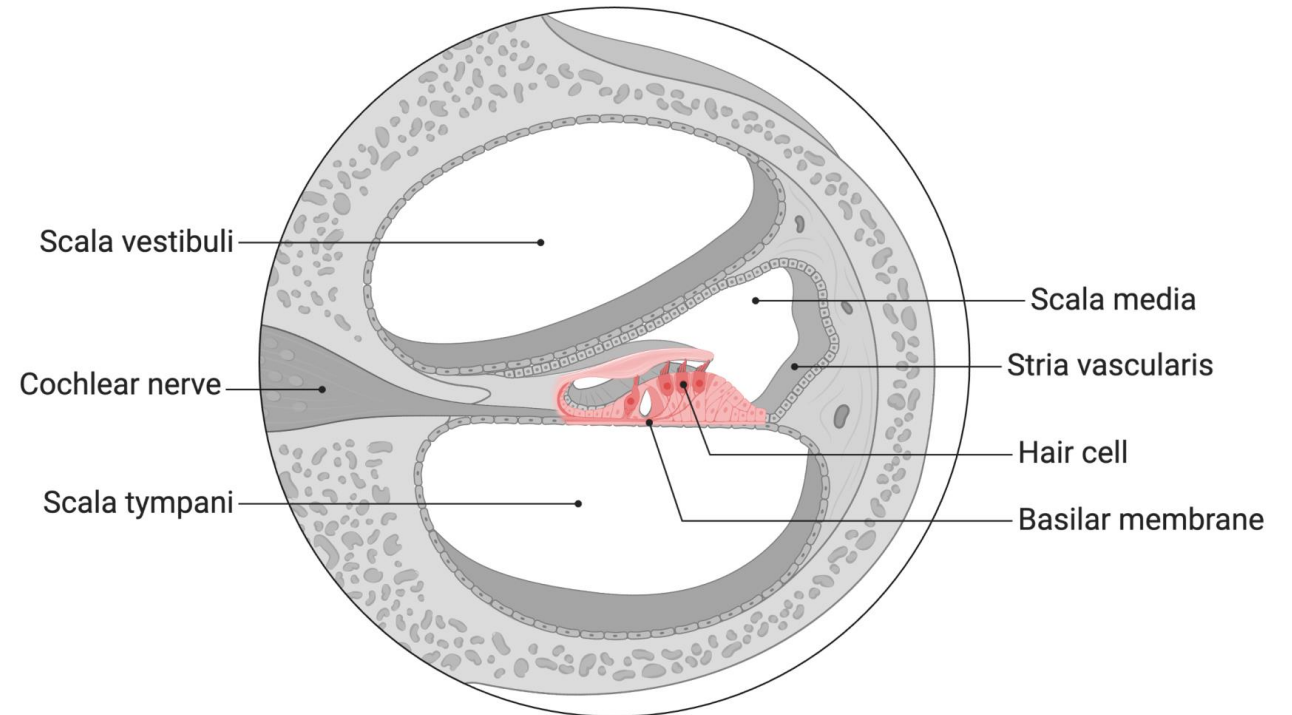
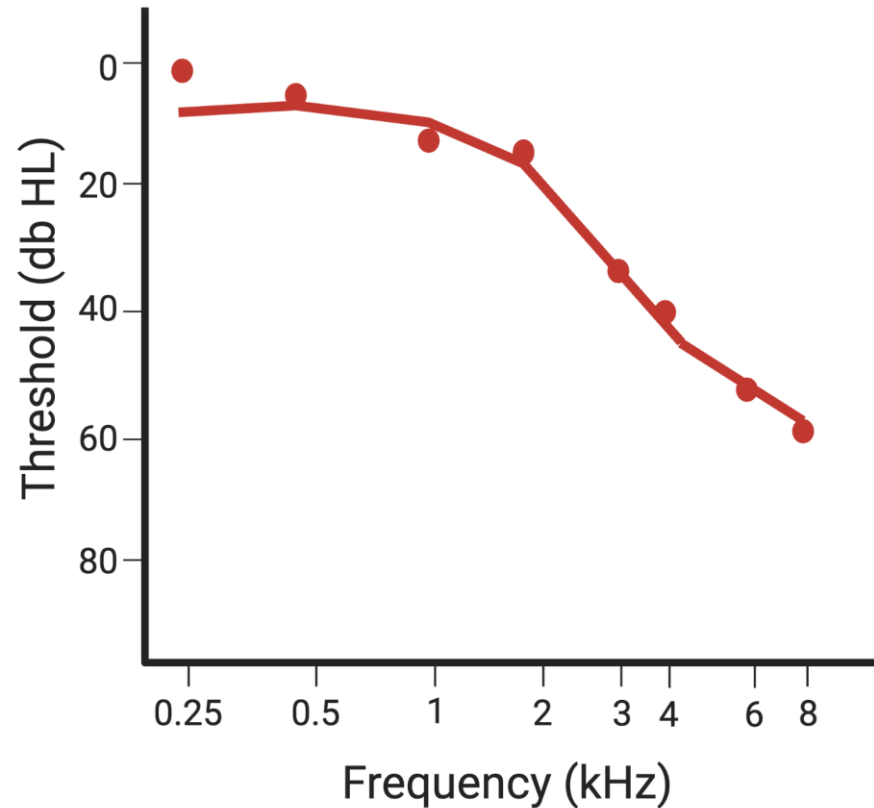
Audiograms measure the softest sounds that individuals can hear at different frequencies



Hearing loss that occurs due to aging processes exhibits a gradual slope in the audiogram



Hearing loss that occurs due to noise exposure exhibits a steep slope in the audiogram



Challenge: Characterization of hearing loss using audiograms is **time consuming**



Samah Ahmed
PhD student

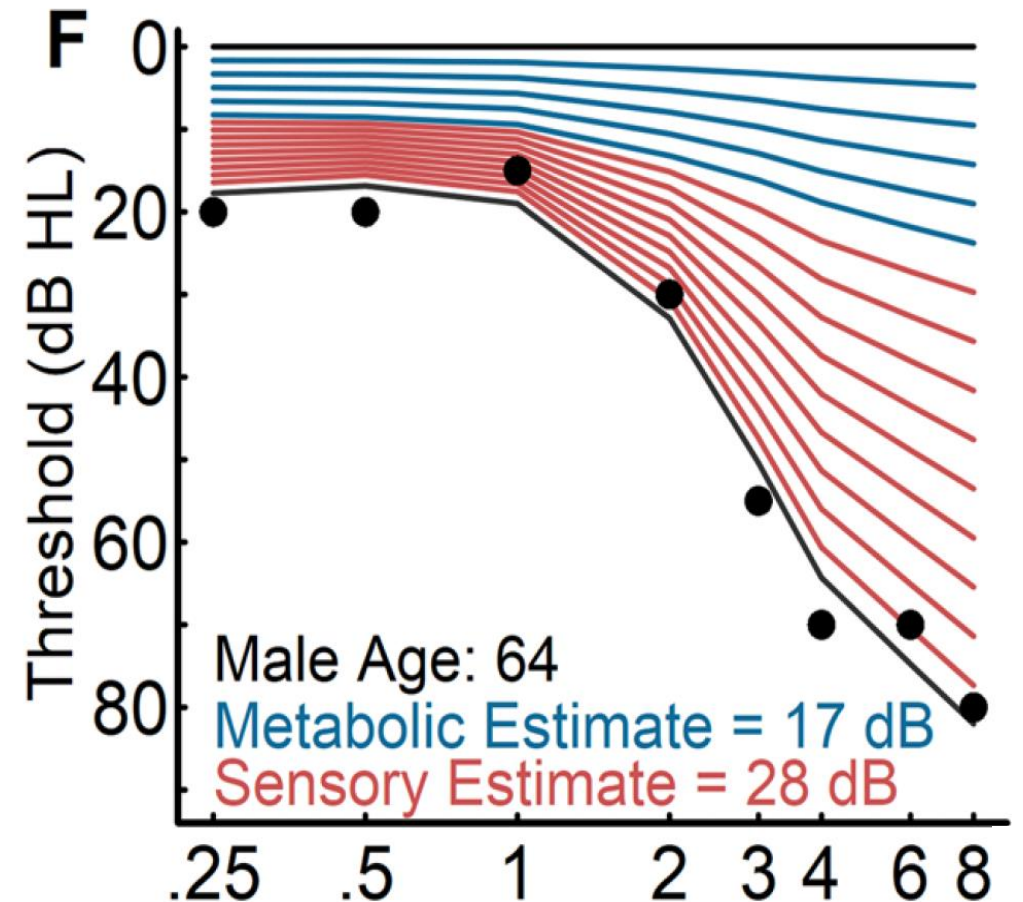
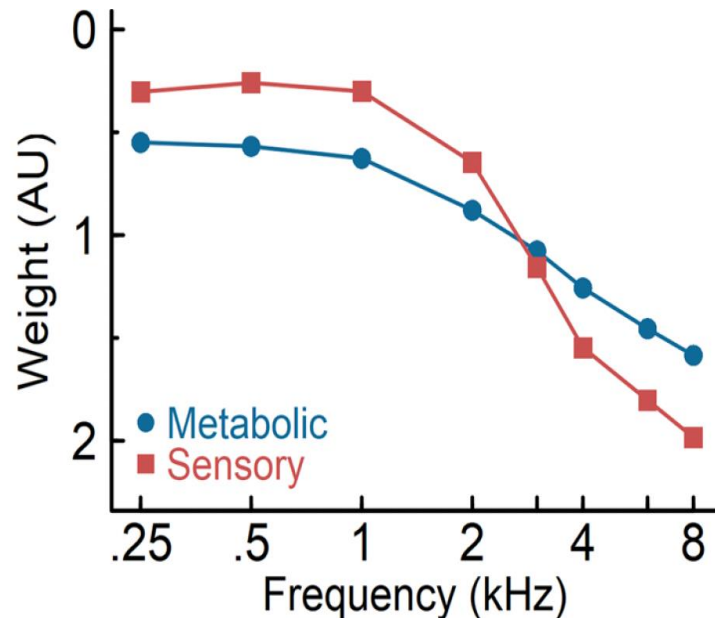
Solution: Use audiograms in combination with **automated phenotyping strategies** to characterize hearing loss for genome-wide association studies

Automated approach used to quantify metabolic and sensory components for each audiogram

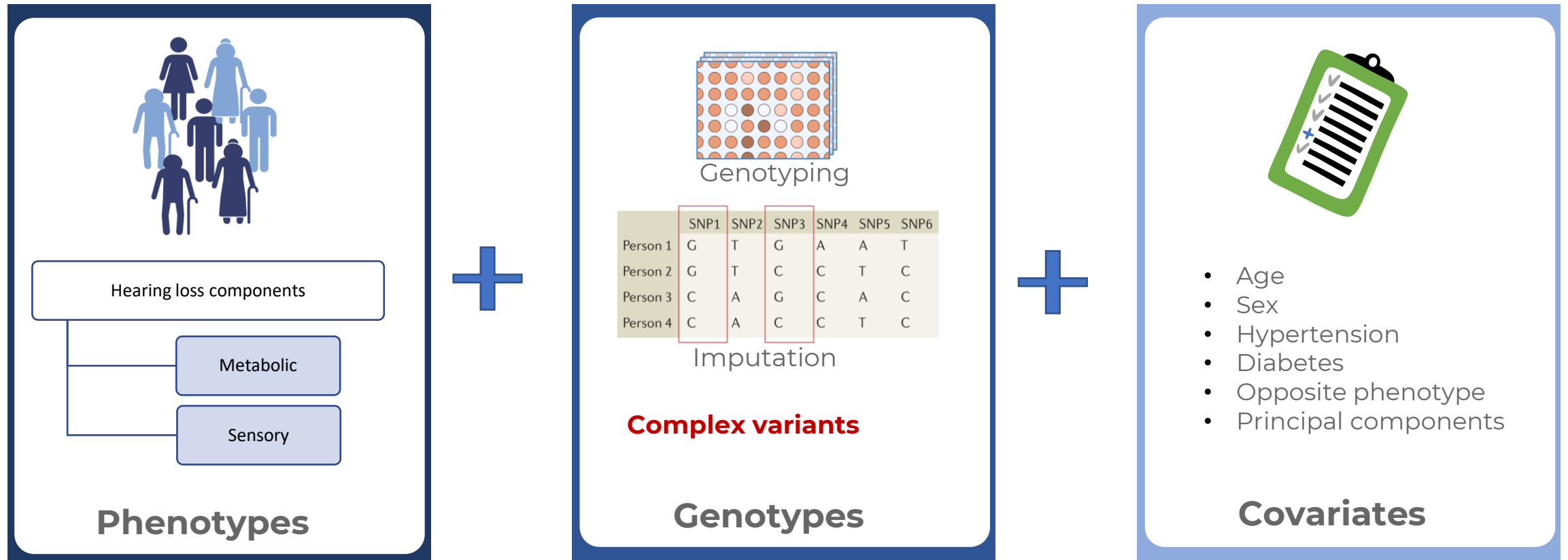
Metabolic and Sensory Components of Age-Related Hearing Loss

KENNETH I. VADEN JR.¹, MARK A. ECKERT¹, LOIS J. MATTHEWS¹, RICHARD A. SCHMIEDT¹, AND JUDY R. DUBNO¹

¹ Hearing Research Program, Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, 135 Rutledge Avenue, MSC 550, Charleston, SC 29425-5500, USA



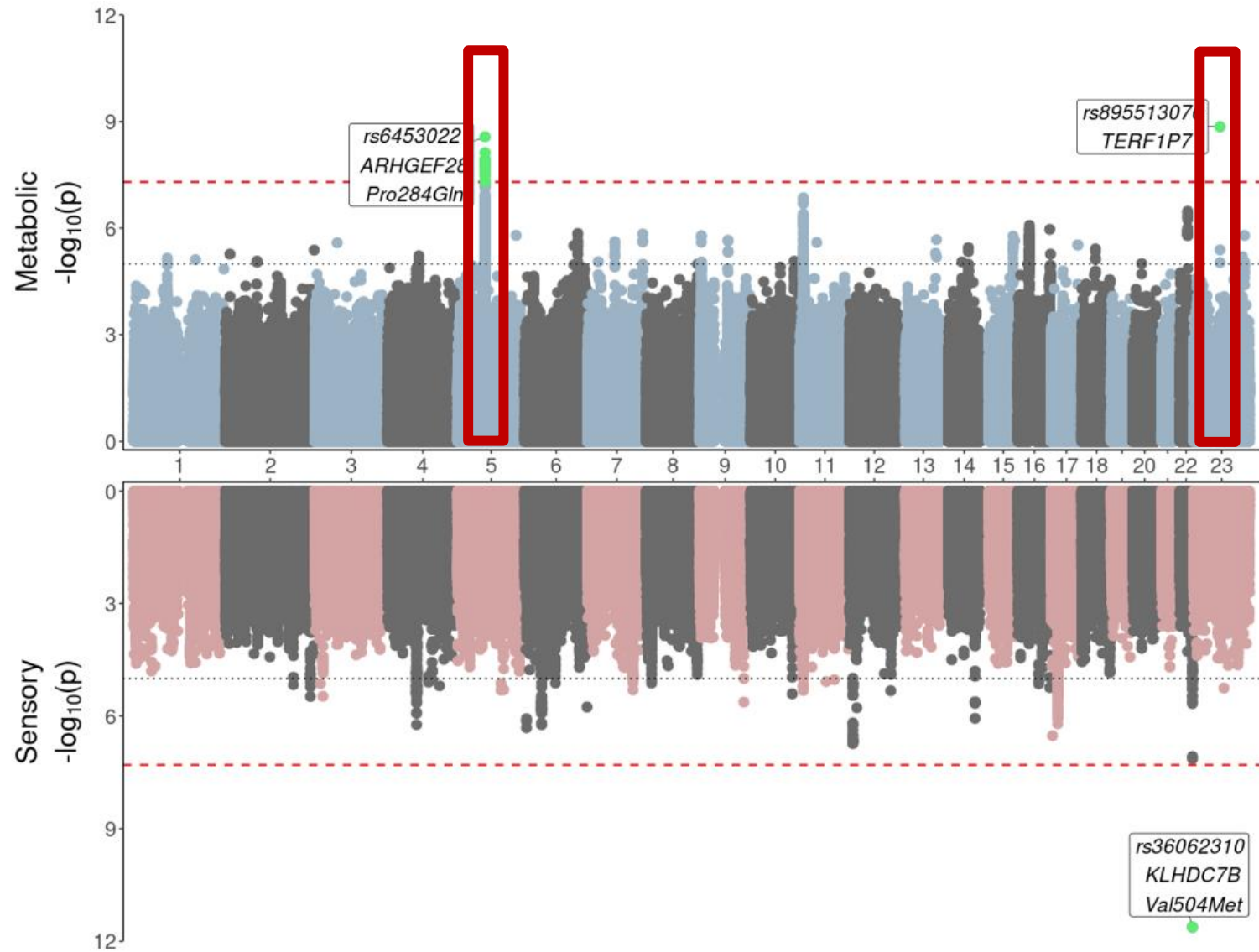
Genome-wide association analyses in the Canadian Longitudinal Study on Aging cohort



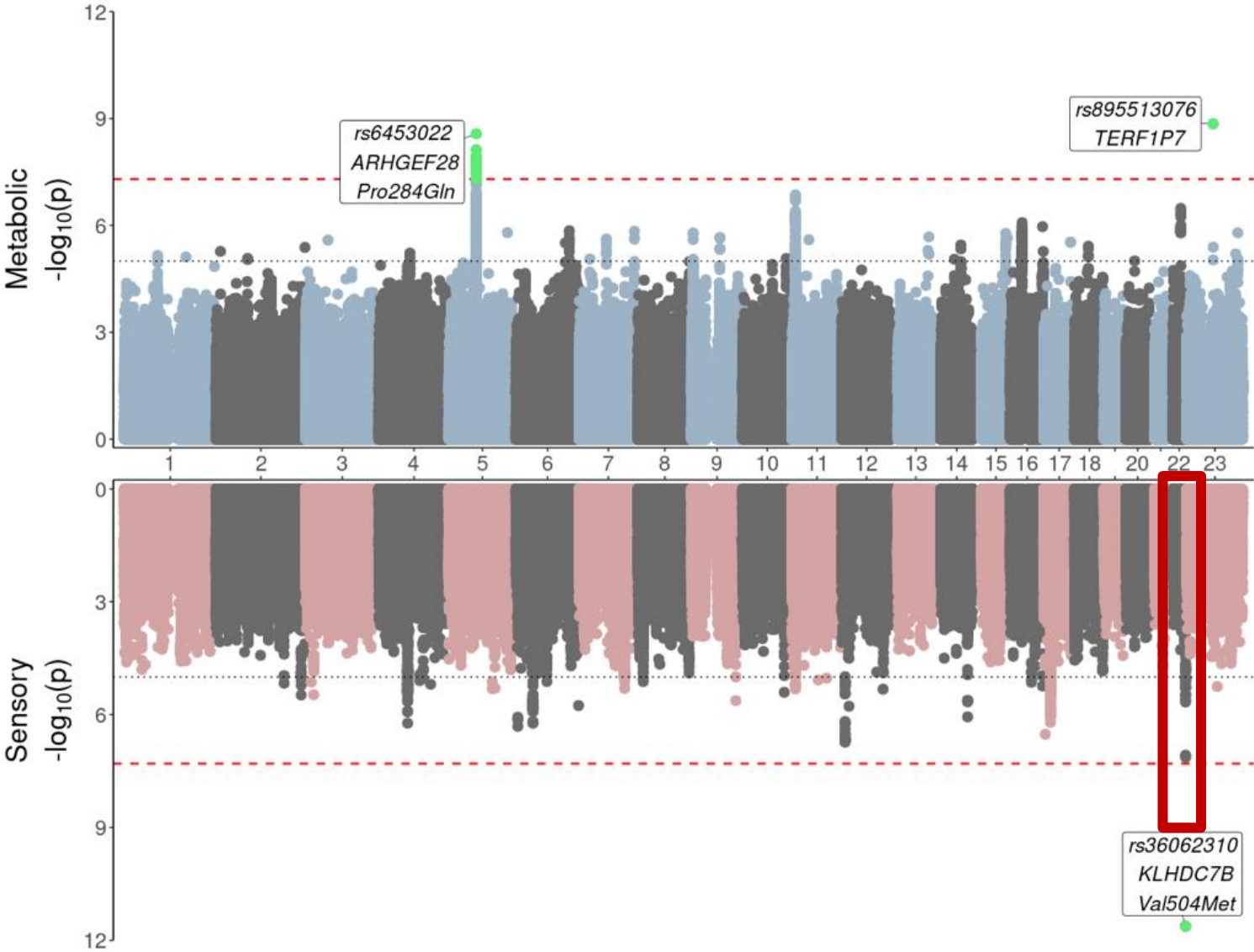
CLSA catalyst grant (Co-PI: Galen Wright): Bioinformatic investigation of previously neglected regions of the genome and their association with age-related hearing loss

Variant-based analyses,
including the X chromosome

Unique loci associated with metabolic hearing loss

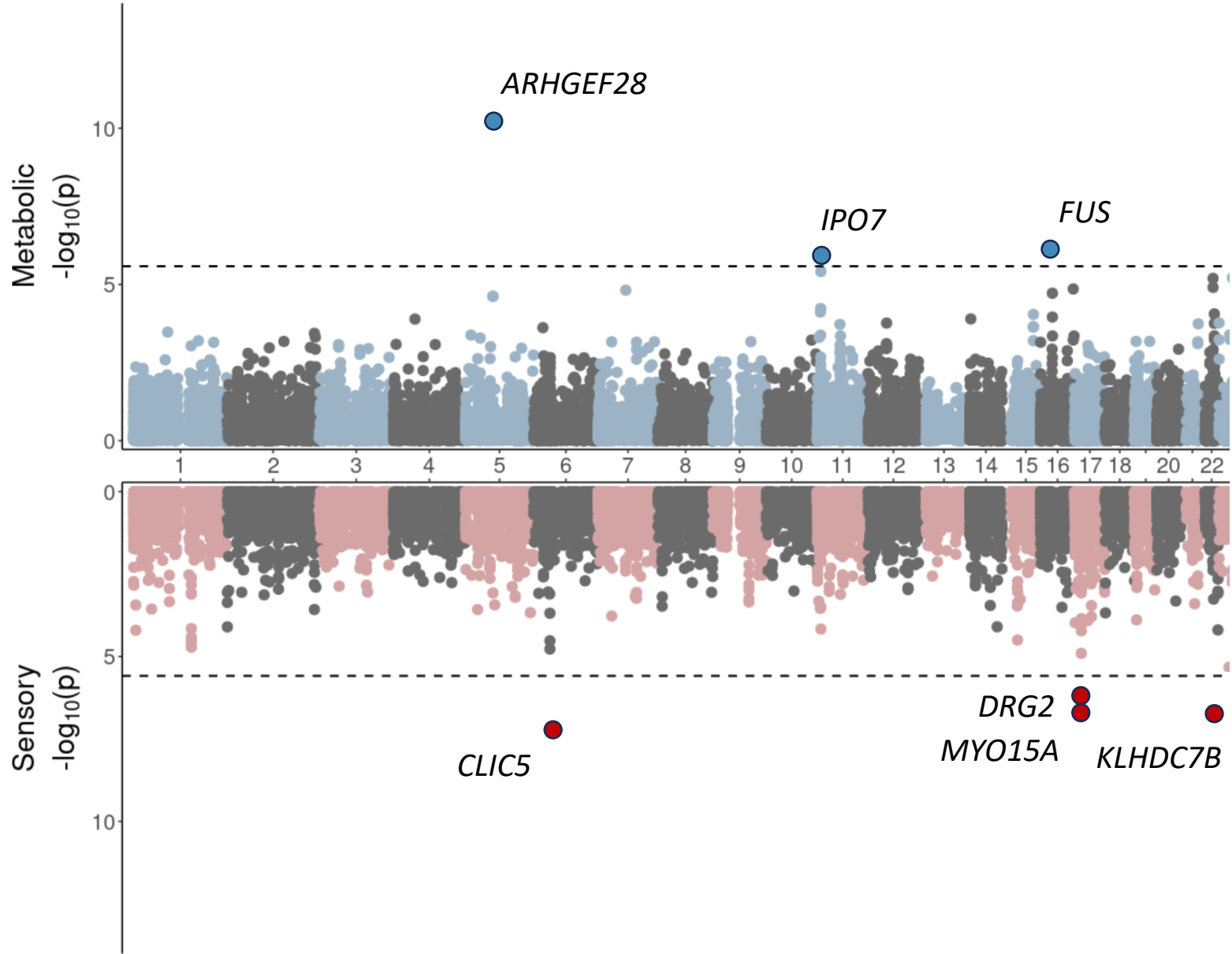


Unique locus associated with sensory hearing loss

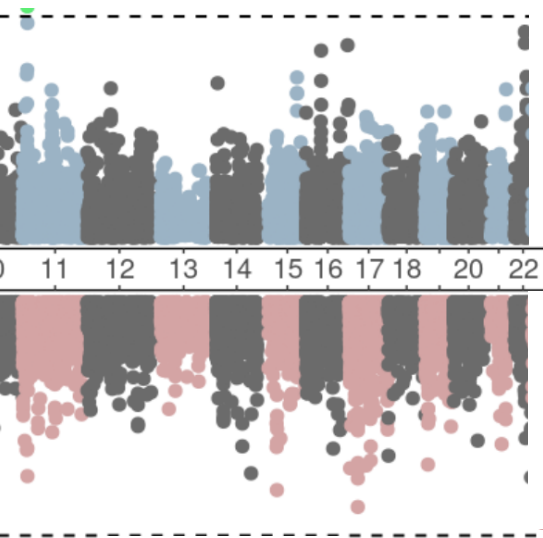


Gene-based analyses

Unique genes associated with metabolic hearing loss

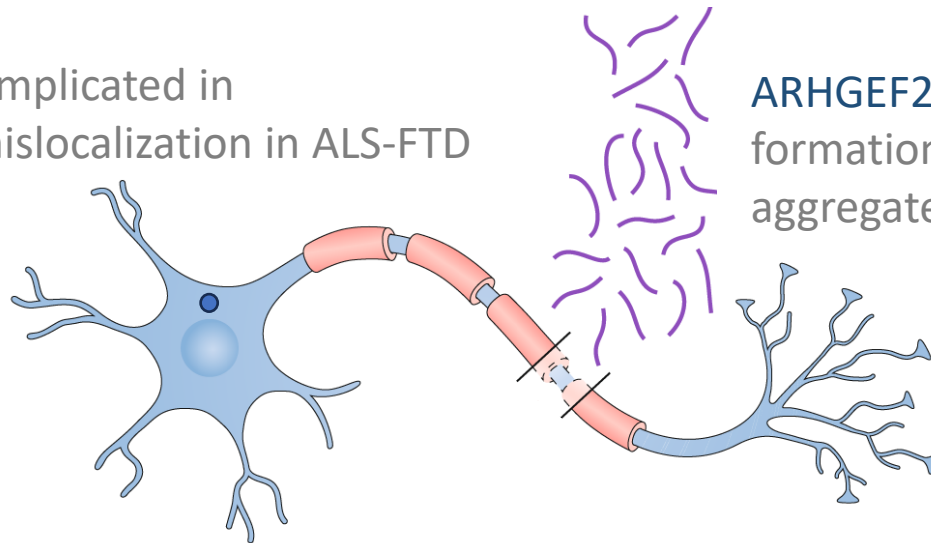


Genes associated with metabolic hearing loss are implicated in ALS frontotemporal dementia



- *FUS*
- *ARHGEF28*
- *IPO7*

IPO7 implicated in *FUS* mislocalization in ALS-FTD

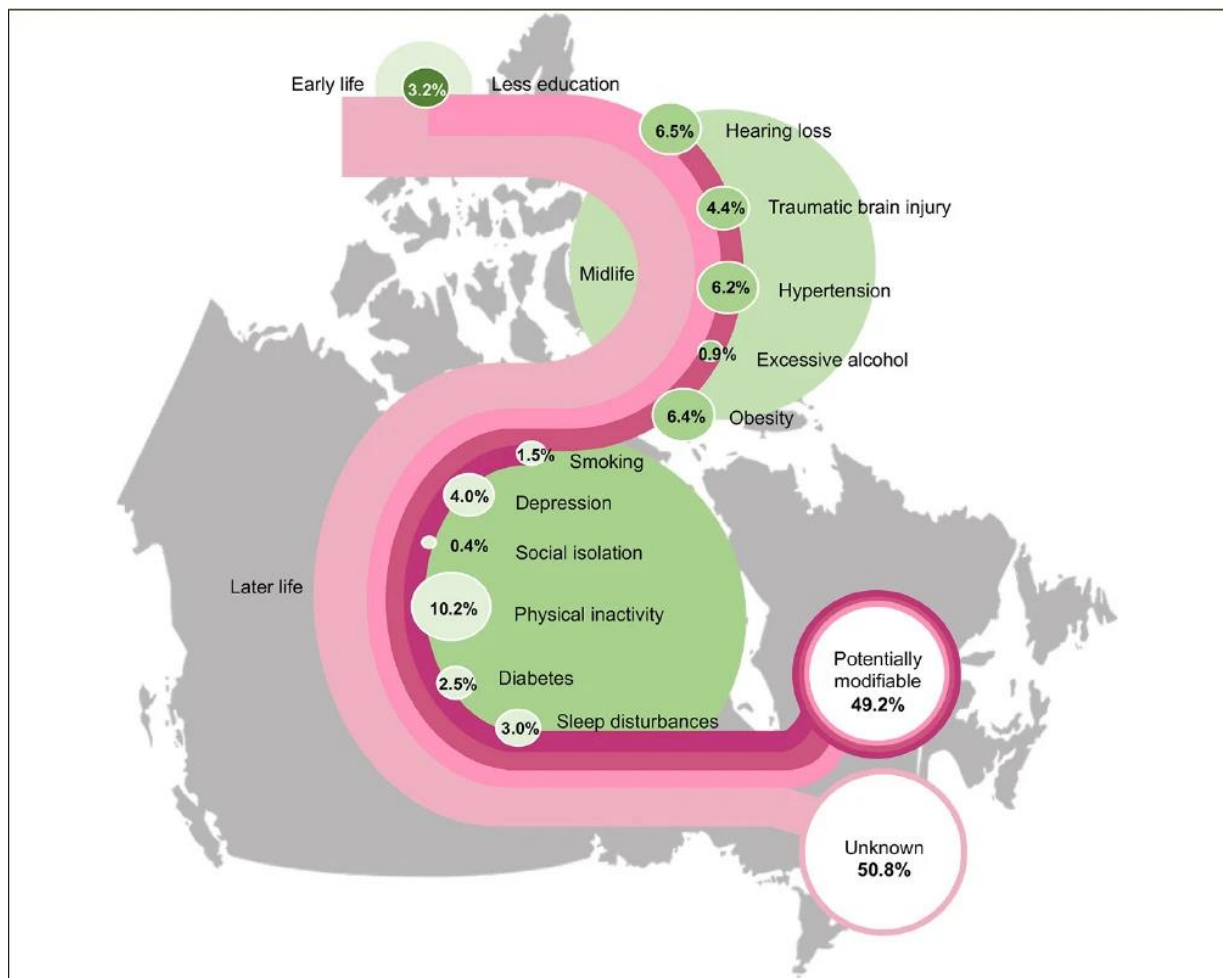


ARHGEF28 implicated in formation of neurofilament aggregates in ALS-FTD

Mead, *et al. Nat Rev Drug Discov.* 2023;22:185-212
Khalil, *et al. Nat Rev Neurol.* 2018;14:577-589

Hearing loss is the largest modifiable risk factor for dementia!

Livingston, *et al. Lancet*. 2020;396:413–446



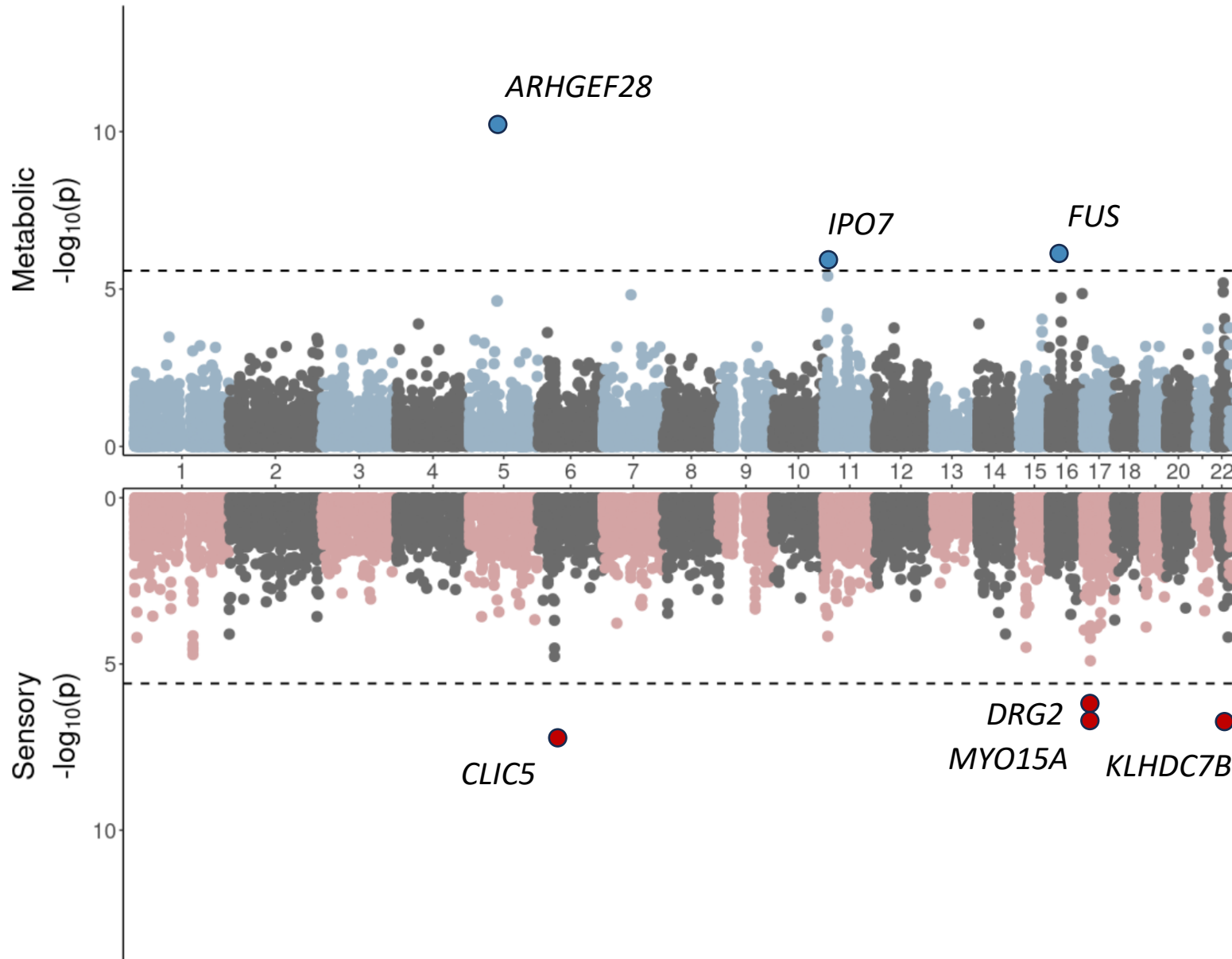
Sun, *et al.* Potentially Modifiable Dementia Risk Factors in Canada: An Analysis of Canadian Longitudinal Study on Aging with a Multi-Country Comparison. *The Journal of Prevention of Alzheimer's Disease*. 2024



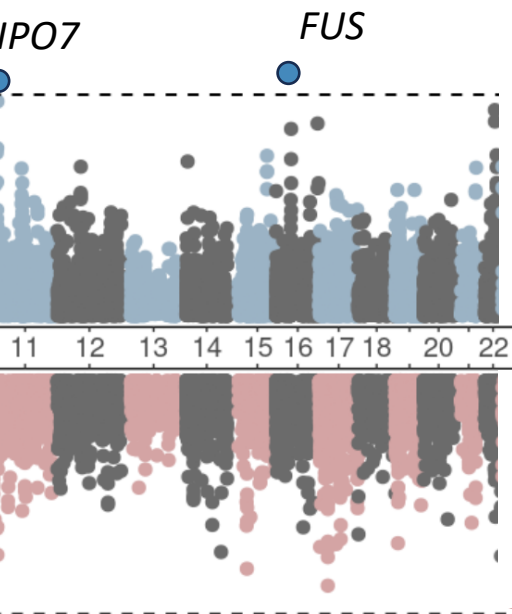
Andy Van Domelen
MSc student

Investigation of the shared genetic pathways underlying metabolic hearing loss and dementia

Unique genes associated with sensory hearing loss



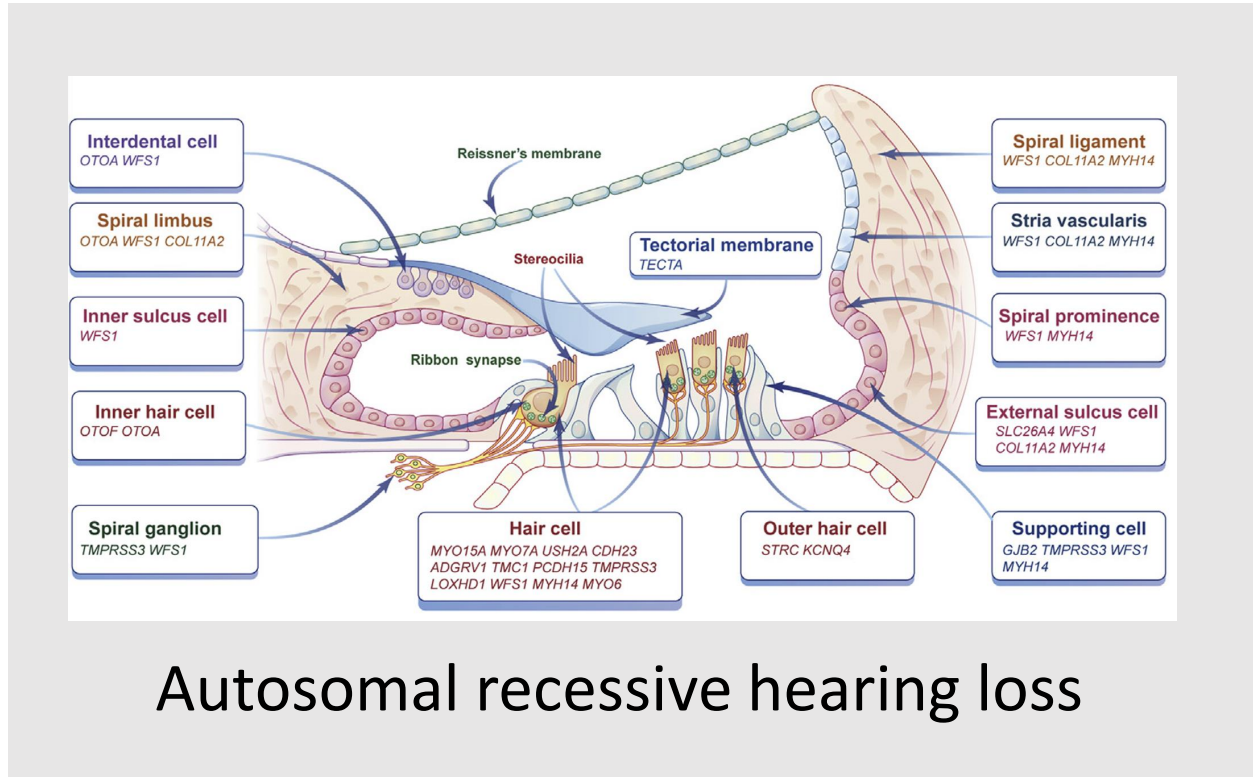
Genes associated with **sensory hearing loss** cause **Mendelian deafness**



- *CLIC5*
- *MYO15A*

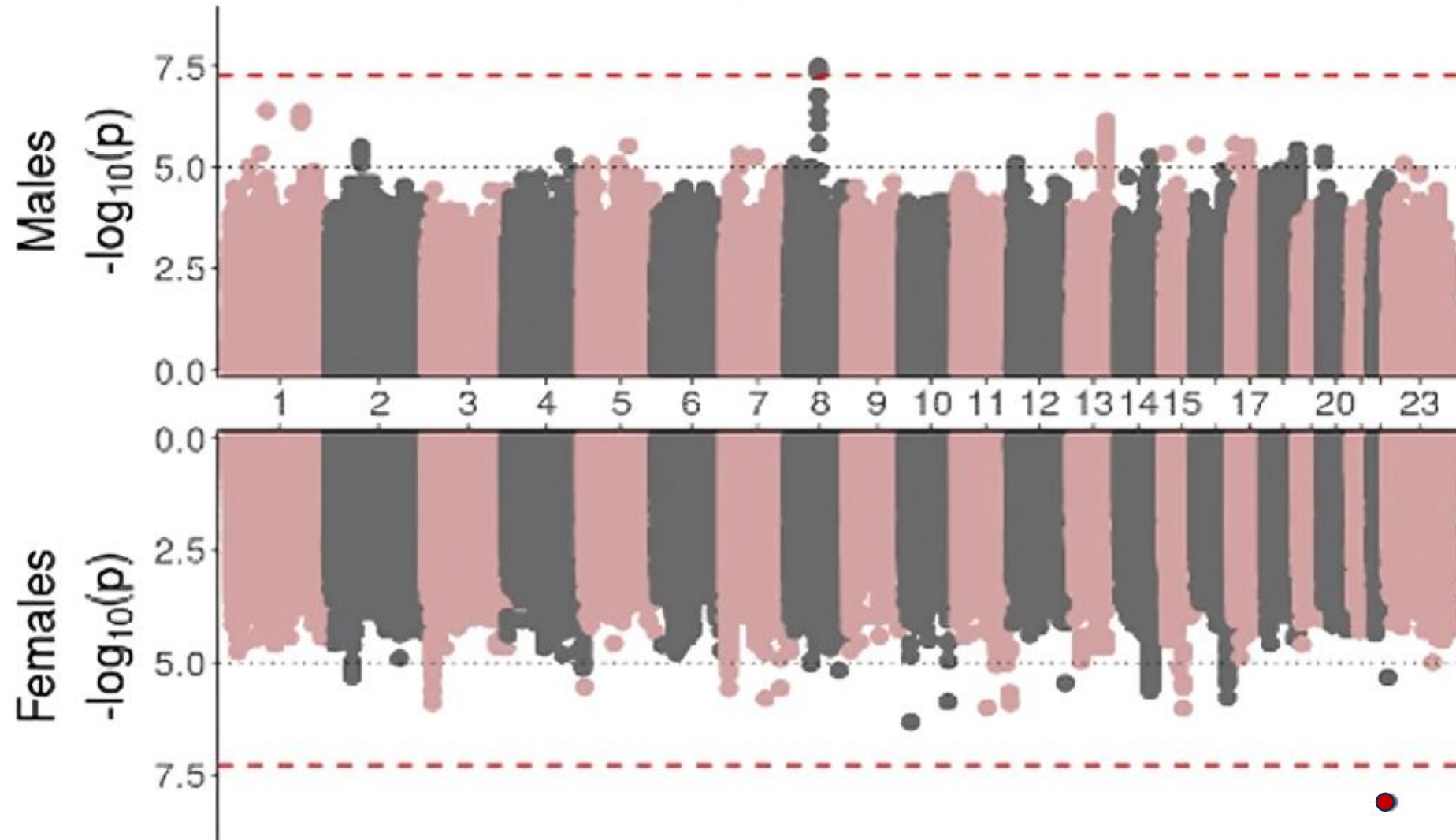
- *DRG2*

- *KLHDC7B*

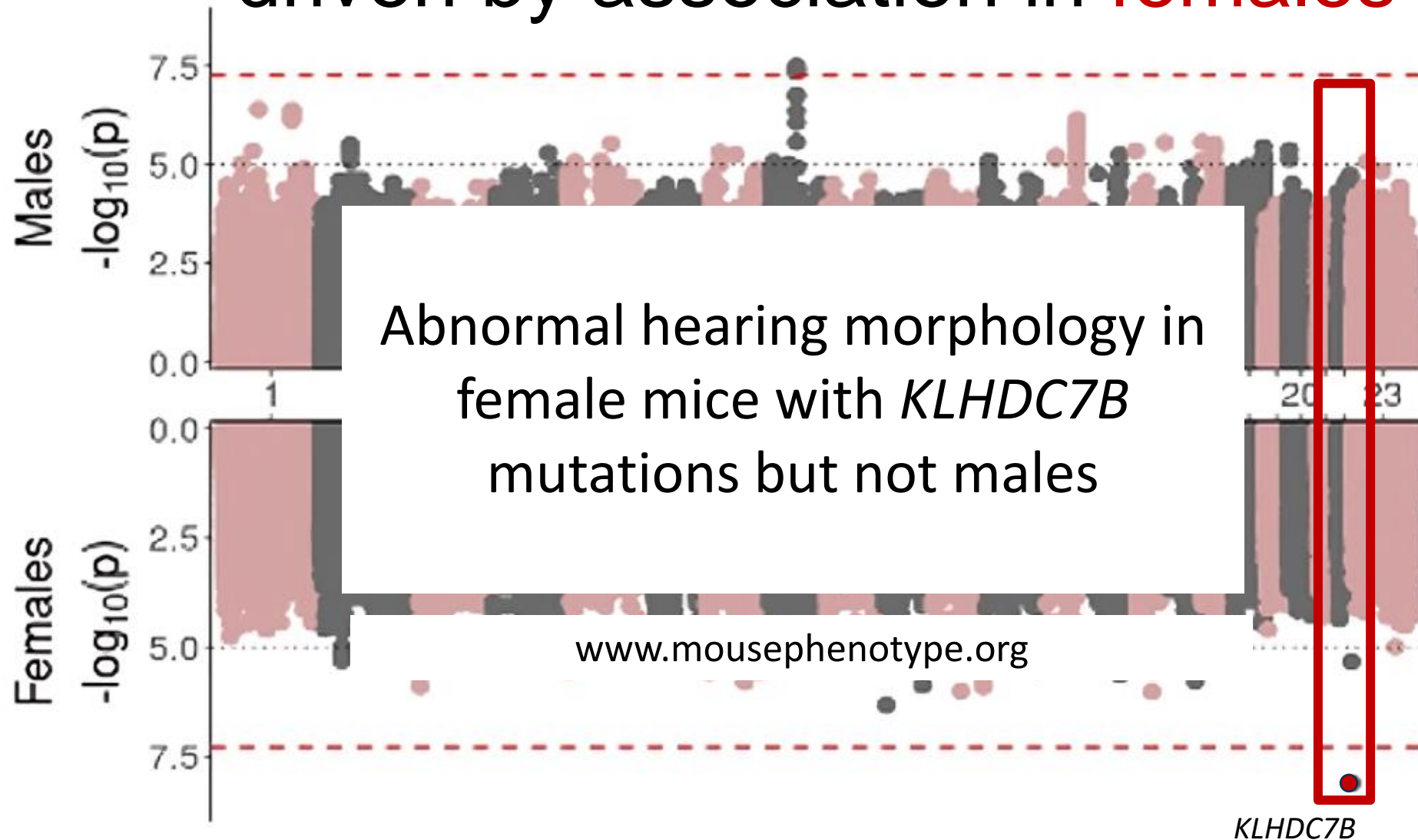


Sex-stratified analyses

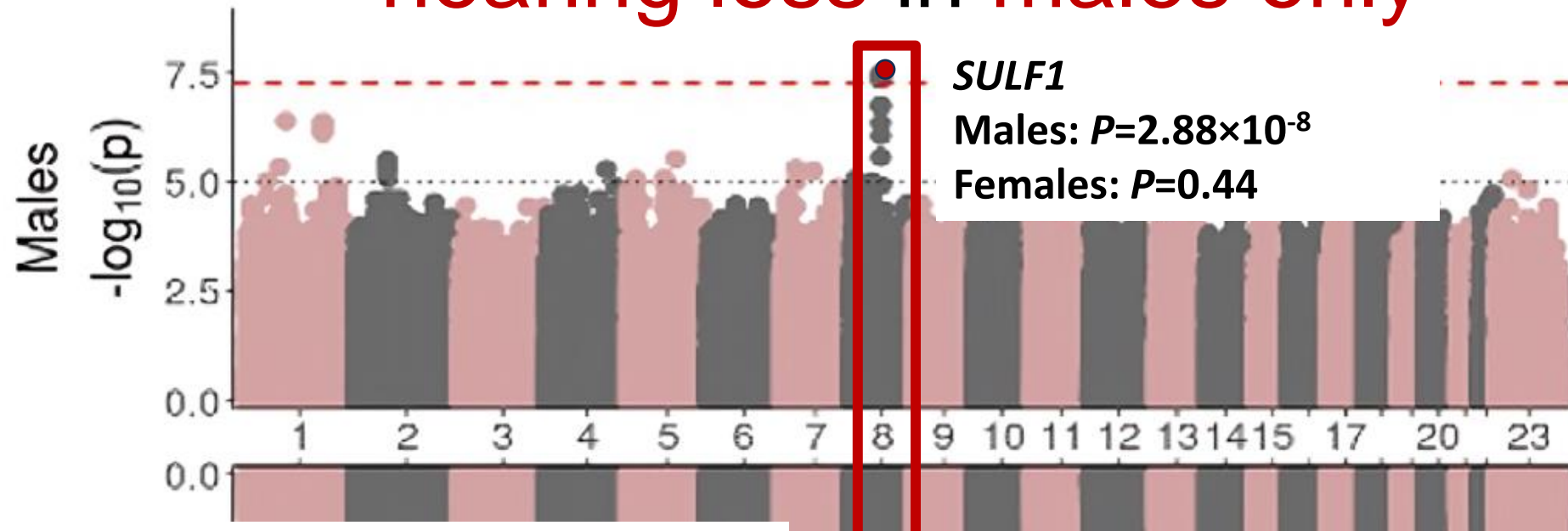
Sex-specific associations for sensory hearing loss



KLHDC7B association with sensory hearing loss driven by association in females



Novel association between *SULF1* and sensory hearing loss in males only



Sulf1 plays an important role in inner ear development in mice

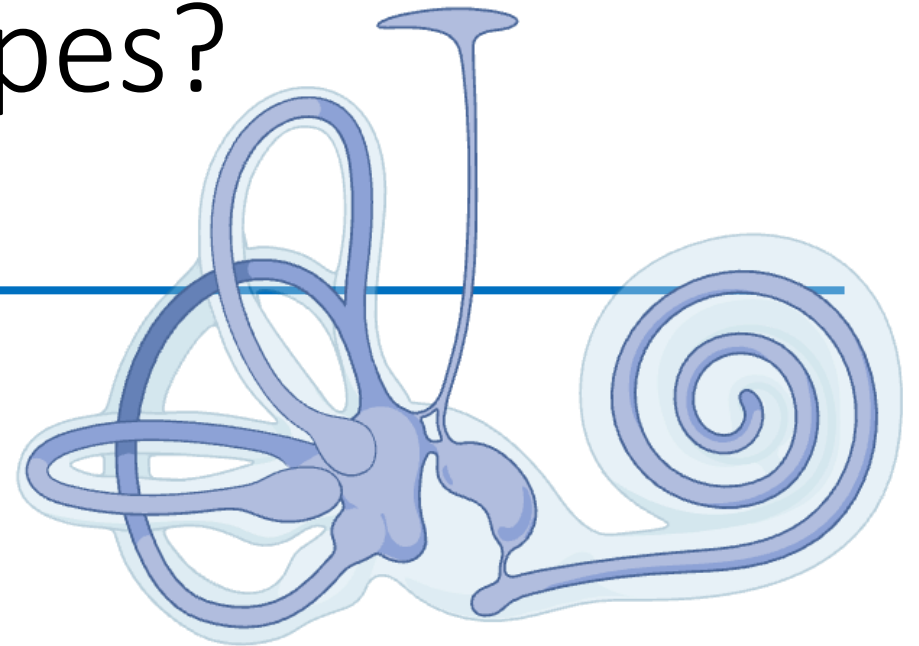
Sulf1 expression increased in aged female mice compared to aged male mice

Freeman *et al. Dev Dyn.* 2015;244:168-80.

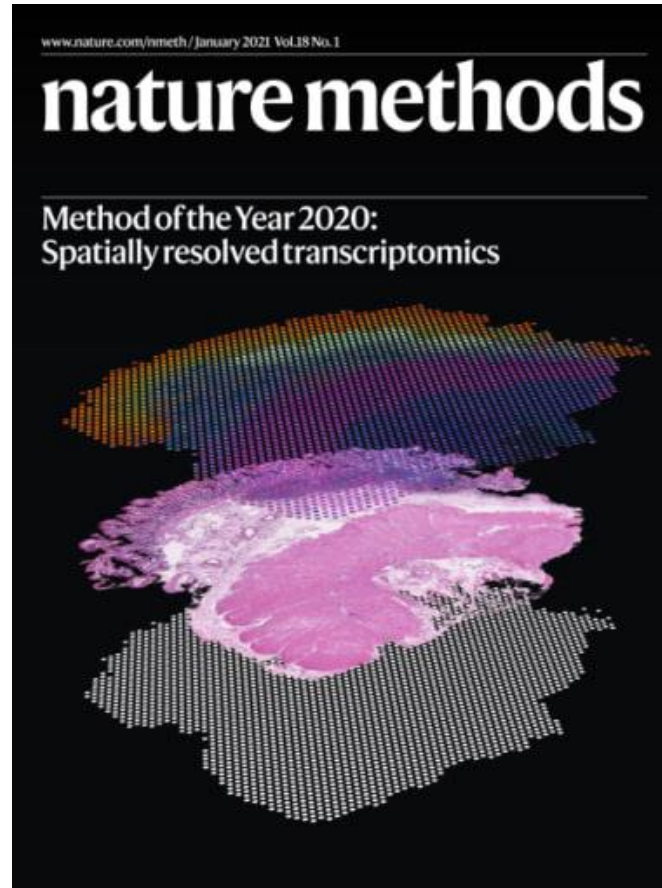
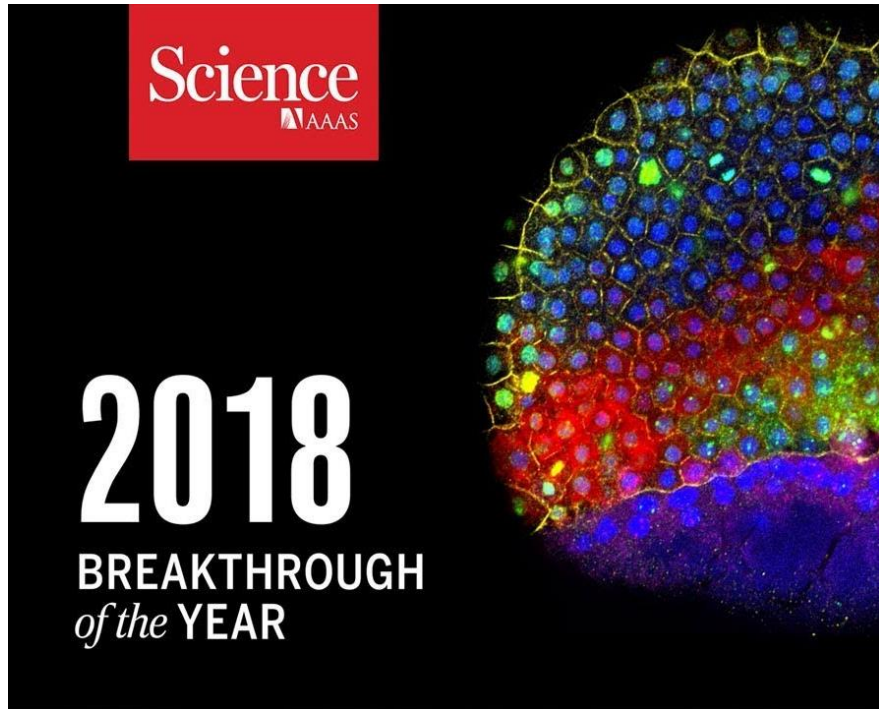
Wang *et al. Aging (Albany NY).* 2018;10:606-21.

Remaining knowledge gaps:

What are the **cellular origins** and **cell specific processes** involved in these distinct hearing phenotypes?



scRNA-seq can provide single cell level insights into the biology of hearing phenotypes



Deanne Nixie Miao
PhD student

Precision Genomics Suite

INNOVATION (Drögemöller, Kowalec, Wright)

Canada Foundation
for Innovation

Fondation canadienne
pour l'innovation



Chromium Xi

Single-cell sequencing

Single-cell library prep
Gene expression, ATAC, etc.



CytAssist

Spatial information

Visium slide set up
Includes new HD slides
Whole transcriptome



Xenium Analyzer

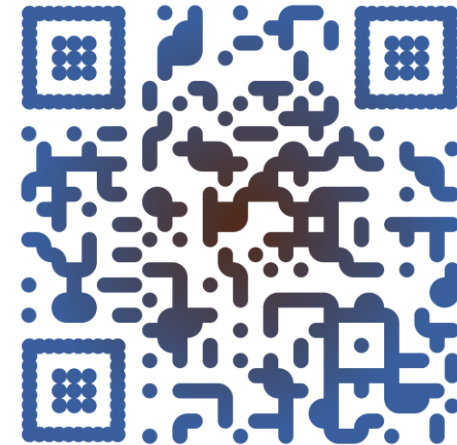
Spatial information

In situ/imaging-based platform
Subcellular resolution
Panel-based (can add custom)

Tools for single-cell and spatial genomics

More info available
via QR code

Experimental / analysis
support



John
Pham



Alana
Lamont

Confirmed **heterogeneous nature** of age-related hearing loss

Uncovered **specific genetic pathways** that are of relevance to **distinct hearing loss** phenotypes

Revealed striking **sex-specific differences**

Improved **understanding** of the genetics
underlying **sensory** and **metabolic hearing loss**

Opened new avenues for future research aimed
at improving **early diagnosis** and **precise
treatment** of hearing loss in older adults

Drögemöller Lab

Samah Ahmed
Deanne Nixie Miao
Andy Van Domelen
John Pham
Alana Lamont
Aiya Beken

Mackenzie Wilke
Emily Allan
Feryal Ladha
Avital Kuznecov
Mary McAuley

Medical University of South Carolina

Judy Dubno
Kenneth Vaden

Sunnybrook Research Institute

Alain Dabdoub
Emilia Luca

University of Manitoba

Janilyn Arsenio
Darren Leitao
Brian Blakley
Galen Wright



Recruiting!

Graduate students/postdocs with expertise or an interest in genomics, bioinformatics, and precision medicine



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Canadian Institutes of Health Research
Instituts de recherche en santé du Canada



Chaires de recherche du Canada
Canada Research Chairs



NSERC
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Research Manitoba



Health Sciences Centre
FOUNDATION



All funds raised stay in Manitoba.