Congenital Hearing Loss

Science Policy & Information Forum on Program Development for Hearing Health

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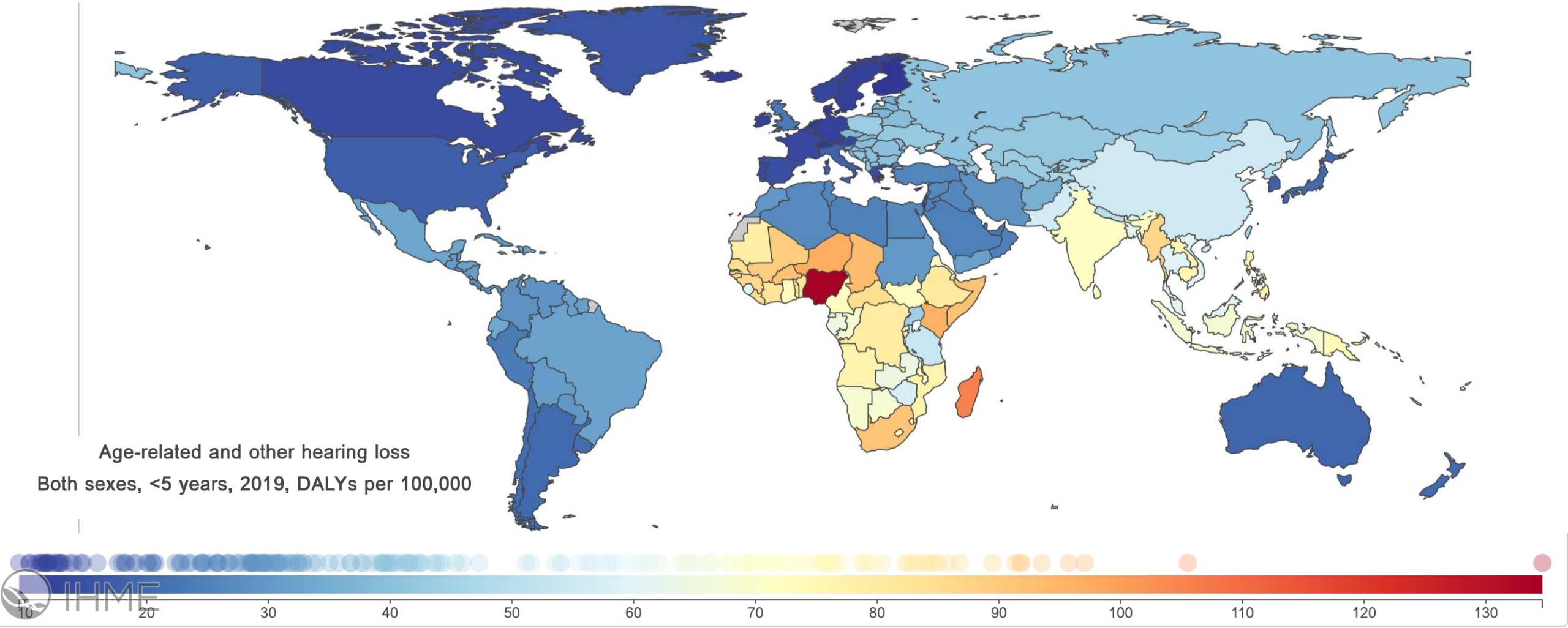
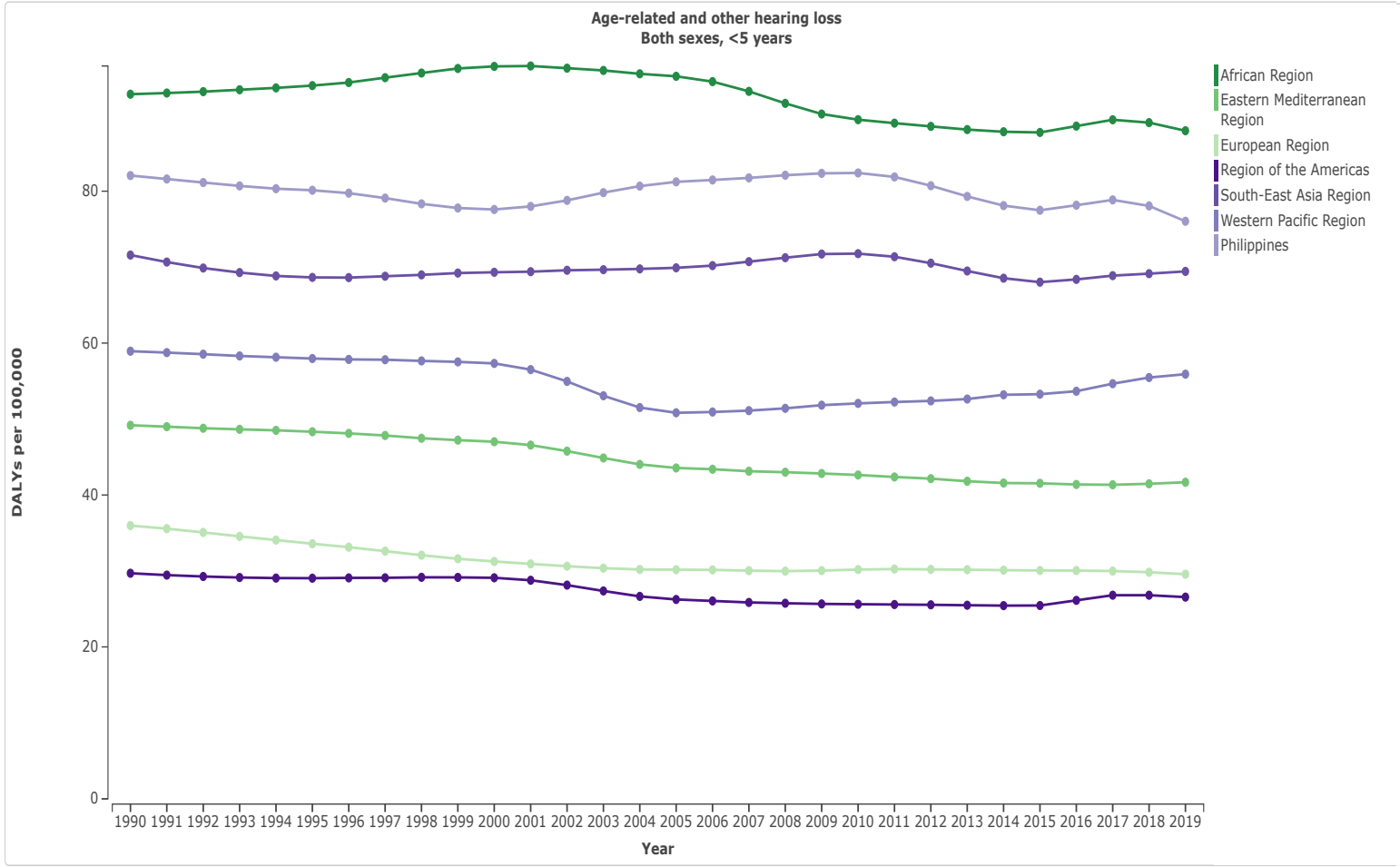
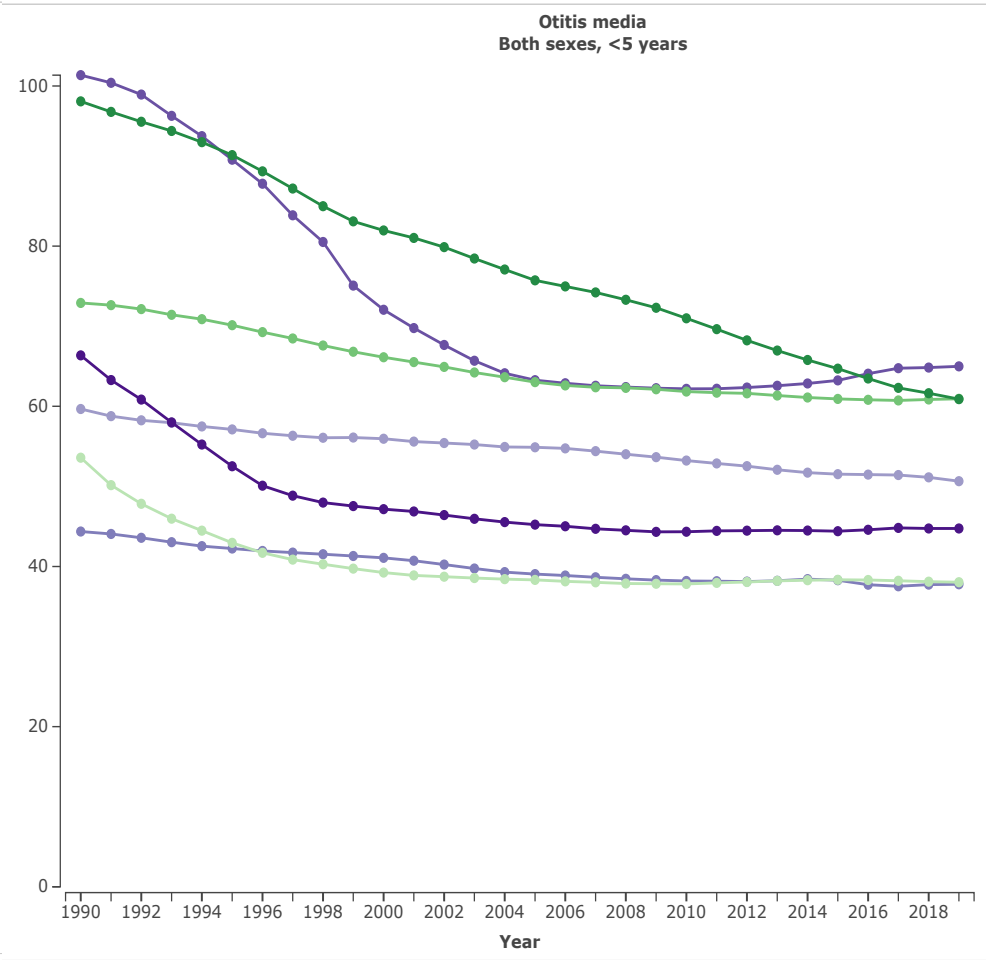
Global Burden of Hearing Loss in Children



Global Burden of Hearing Loss & Otitis Media

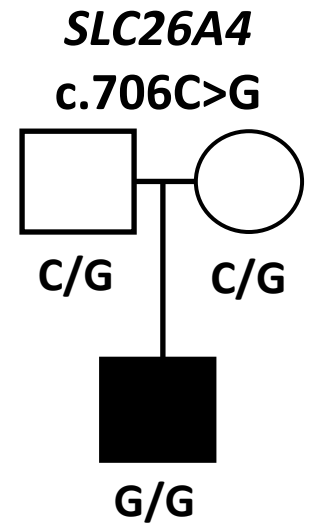




Congenital Hearing Loss in the Philippines

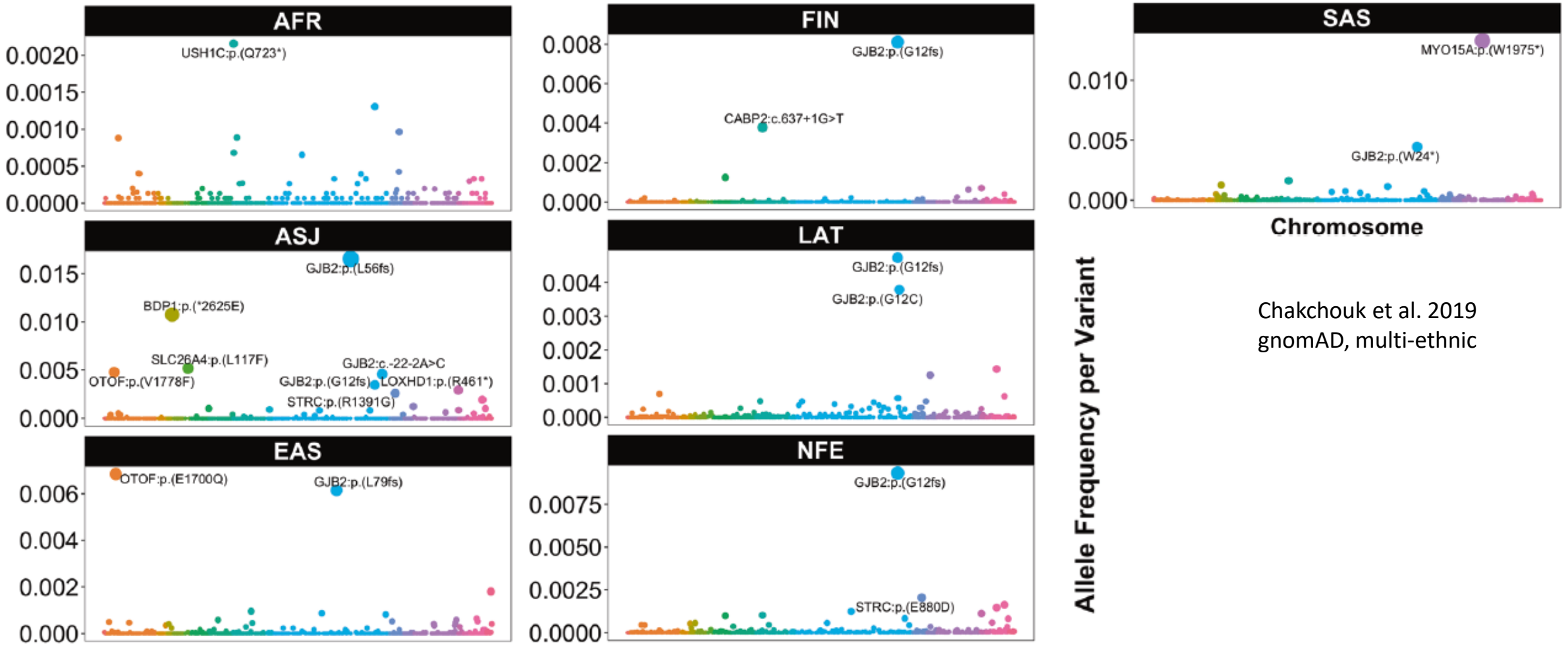
- UNHS and Intervention Law (RA9709) passed in 2009
  - 7 seminal papers from Chiong et al.
- Ong et al. 2020: all HL 3.6%; bilateral profound HL 4 in 1000
  - Better cost analysis for AABR alone
- Newall et al. 2019, 2020: n=2275, moderate-profound HL 7.5% <18y.o.
  - Associated with middle ear condition, socioeconomic status
  - Poor hearing aid outcomes, need follow-up care, better devices
- Emmett et al. 2019: need for 2x audiologists, +70 speech therapists
  - Lifetime CI costs ~$84K cheaper than other Southeast Asian countries
  - CI is cost-effective in the Philippines, deaf education very cost-effective

Genetic & Non-genetic Hearing Loss



- **Genetic HL accounts for 50-60% of congenital HL**
  - Syndromic HL examples: Usher, Waardenburg
  - **>80% of genetic HL is nonsyndromic**
  - For nonsyndromic, majority are autosomal recessive (AR)
    - Greater proportion in populations with high consanguinity rates
  - The rest are autosomal dominant (AD), sex-linked, mitochondrial
- HL prevalence increases with age (genetic, infection, noise, ototoxicity)
  - cCMV 6 per 1000 in USA, HL can be latent, screening validity (Haller et al. 2021)
  - Congenital rubella-HL 1.7% of live births in the Philippines (Lopez et al. 2017)

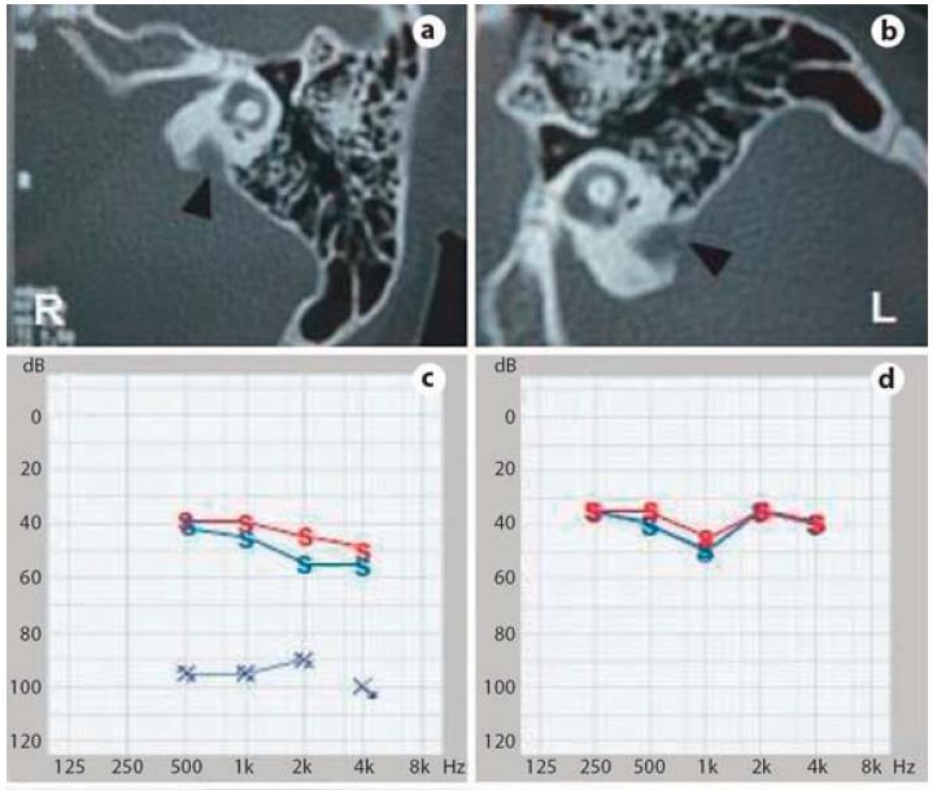
Population-Specific HL Genetic Variants



Chakchouk et al. 2019
gnomAD, multi-ethnic

HL Genetic Variants in Filipinos - 1

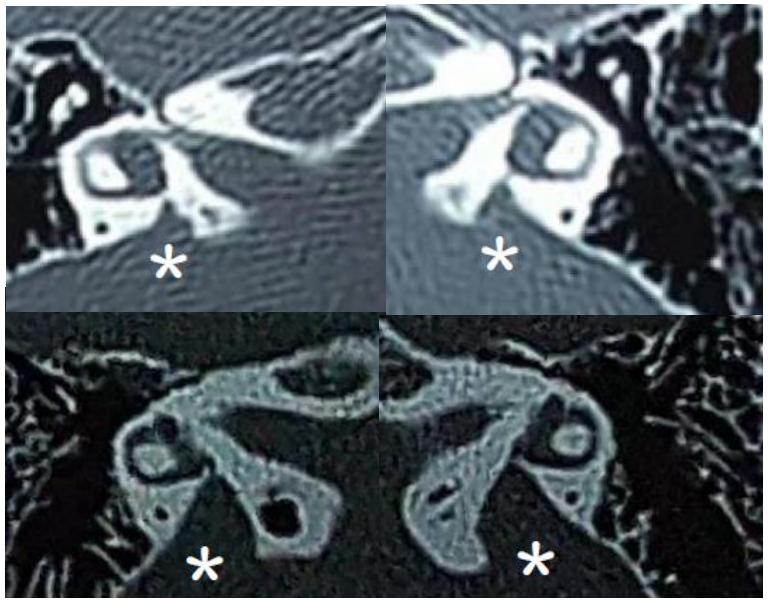
GJB2 Variants and Auditory Outcomes among Filipino Cochlear Implantees



- Chiong et al. 2013
- 30 Filipino CI patients
- PEACH scores better with longer CI use
- *GJB2* Sanger sequencing
- 1/30 = 3.3% *GJB2*+
- One male of mixed descent with *GJB2* c.35delG/c.235delC
- Good CI outcome
- Brother also required CI

HL Genetic Variants in Filipinos - 2

The *SLC26A4* c.706C>G (p.Leu236Val) Variant is a Frequent Cause of Hearing Impairment in Filipino Cochlear Implantees

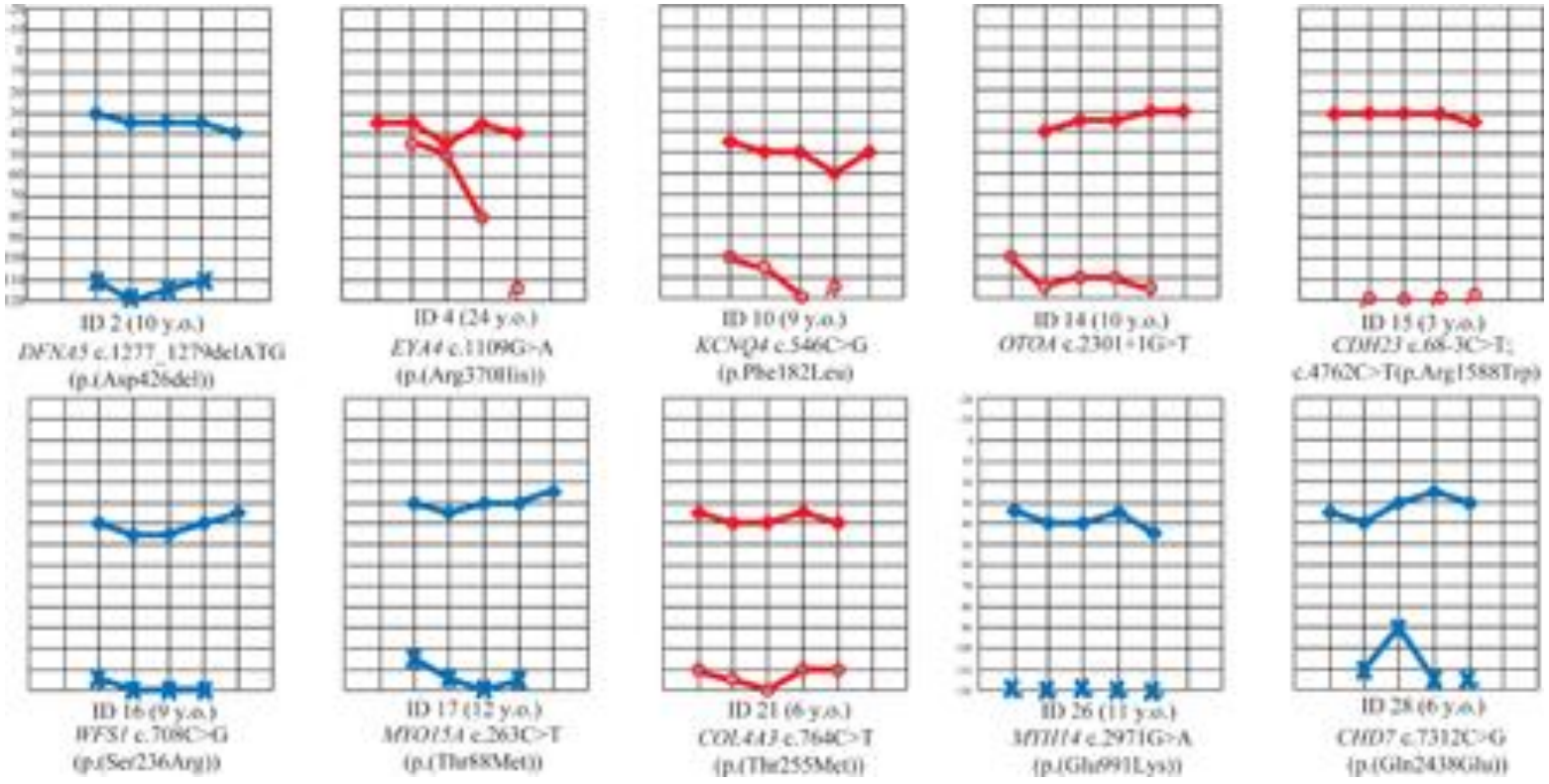


- Chiong et al. 2018
- Sanger-seq of *SLC26A4* coding exons and exome seq for 29 CI patients
- 4/30 = 13.3% homozygous for *SLC26A4* c.706C>G (p.Leu236Val)
- No other HL variants identified in exome data of these 4 patients
- MAF Lat=0.0003, EAS=0.0001
- All 4 *SLC26A4*+ with worse pre-CI dB and bilateral EVA
- *SLC26A4*+ median post-CI 37.5dB

HL Genetic Variants in Filipinos - 3

Exome sequencing reveals novel variants and unique allelic spectrum for hearing impairment in Filipino cochlear implantees

CLINICAL GENETICS



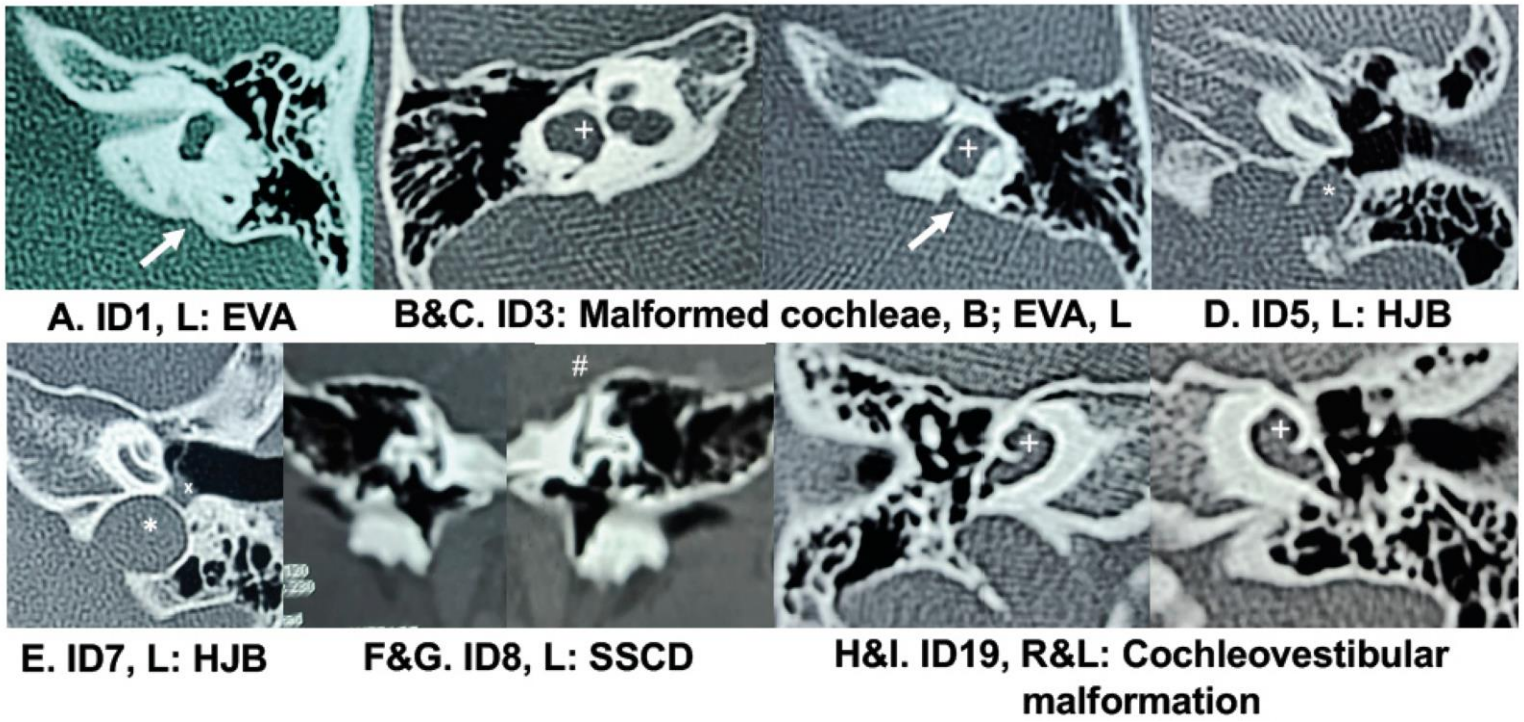
- Truong et al. 2019
- Seven novel variants
- *EYA4:* R EVA > dizziness
- *COL4A3:* check for renal
- *MYH14:* developmental delay, left foot inversion
- *CHD7:* CHARGE
- *WFS1:* white matter disease, mild motor delay
- Ave. post-CI 38 dB

HL Genetic Variants in Filipinos - 4

Identification of Novel Candidate Genes and Variants for Hearing Loss and Temporal Bone Anomalies

genes

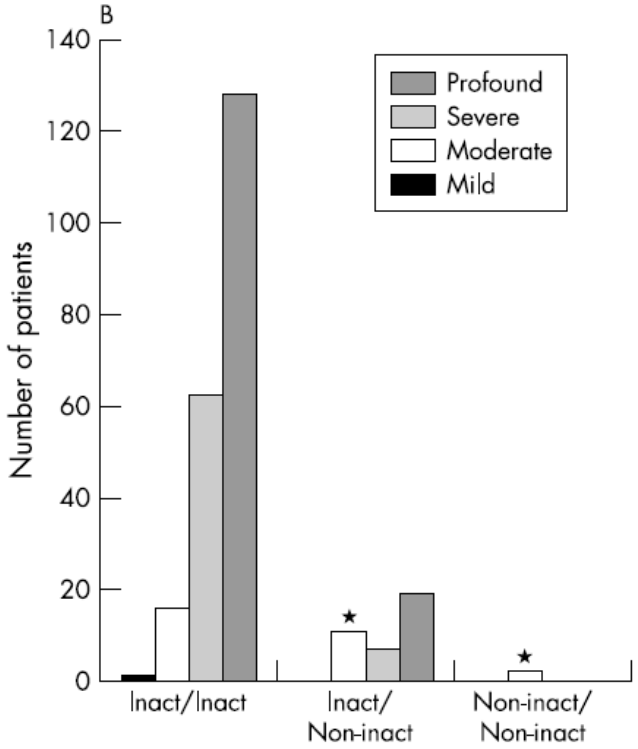
- Santos-Cortez et al. 2021
- Reviewed 15 unsolved exomes
- 21 variants in 17 genes
- 11 novel variants
- 14 known HL and neurodevelopmental genes
- 3 candidate genes *IST1, CBLN3, GDPD5*
- Poorer CI outcomes with *IST1* and *MYO15B* variants

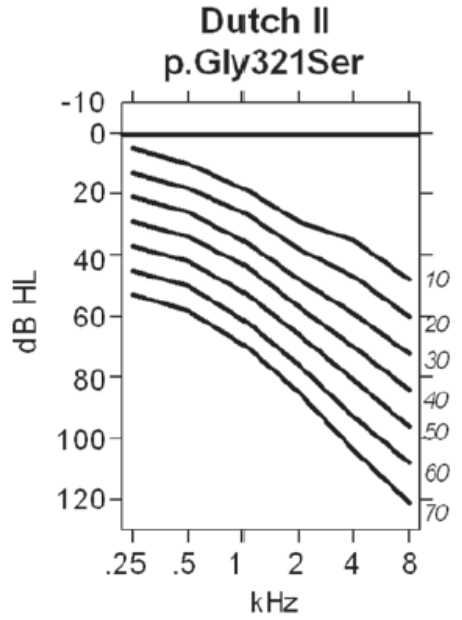


A. *DSPP* B-C. *LMX1A/COL2A1* F-G. *COL11A1/TECTA* H-I. *MYO18B*

Clinical Implications

- Genetic counseling
  - Risk assessment for additional children, other relatives
  - HL severity depending on gene, variant (*GJB2*, Cryns et al. 2004)
  - Later-onset HL (*KCNQ4,* de Heer et al. 2011)
  - Cochlear implant outcomes
- Search for additional clinical features for management
  - *CDH23 & MYO7A* (n=5 NSHL at 3-8 y/o)
    - Usher syndrome type ID or 1B, profound congenital HL, vestibular dysfunction, retinitis pigmentosa by age 10
    - autosomal recessive nonsyndromic HL DFNB12/DFNB2
    - autosomal dominant nonsyndromic HL DFNA11



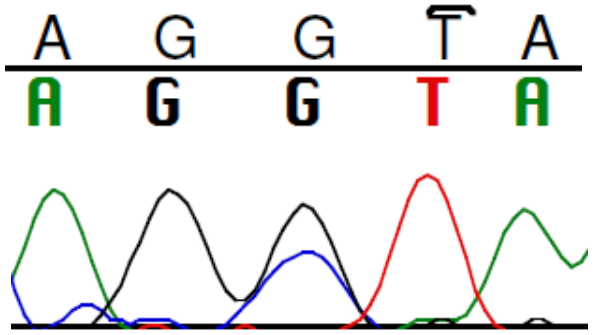


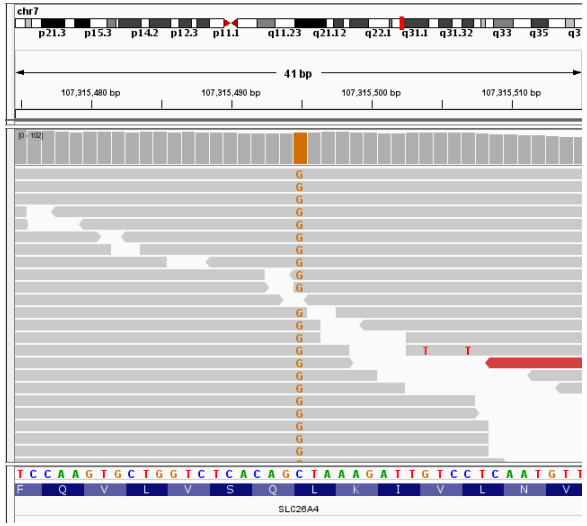
Clinical Implications

- Associated inner ear malformations
  - *POU3F4:* X-linked mixed HL, perilymphatic gusher
  - *CHD7:* CHARGE syndrome, auricular and cochleovestibular defects, sensorineural/mixed HL, atretic cochlear nerve canal
  - *LMX1A:* malformed cochleae in mice
- Etiology-based diagnosis
  - Multiple genes/variants
  - Need for team approach: ENT, audiologist, geneticist, genetic counselor, ophthalmologist/other specialists

Testing for Genetic Variants

BY GENE/ VARIANT	ACROSS GENOME
Sanger sequencing Covers <1000 bp of a gene at a time	**Exome sequencing** All coding exons of ~20,000 genes (1% of human genome)
Targeted panel Known HI genes tested	**Whole-genome sequencing (WGS)** 3 billion base pairs in human genome





***SLC26A4* c.706C>G (exon 6)**

Screening for Genetic Variants, Mendelian/HL

- Annotate variants: ANNOVAR, SnpEff, VEP
- Filter/select single nucleotide variants based on assumptions
  - Known HL genes (human, mouse)
  - Minor allele frequency or MAF (rare <0.005 AR, <0.0001 AD)
    - gnomAD, ExAC, 1KG, GME, GenomeAsia100K
  - Bioinformatic prediction
    - dbNSFP: CADD, PolyPhen-2, SIFT/PROVEAN, MutationAssessor, MutationTaster, FATHMM, mLR/mSVM; M-CAP; REVEL; GWAVA
- ACMG-AMP Classification: benign, likely benign, VUS, likely pathogenic, pathogenic
  - Loss-of-function, de novo, known, co-segregation in family, population MAF

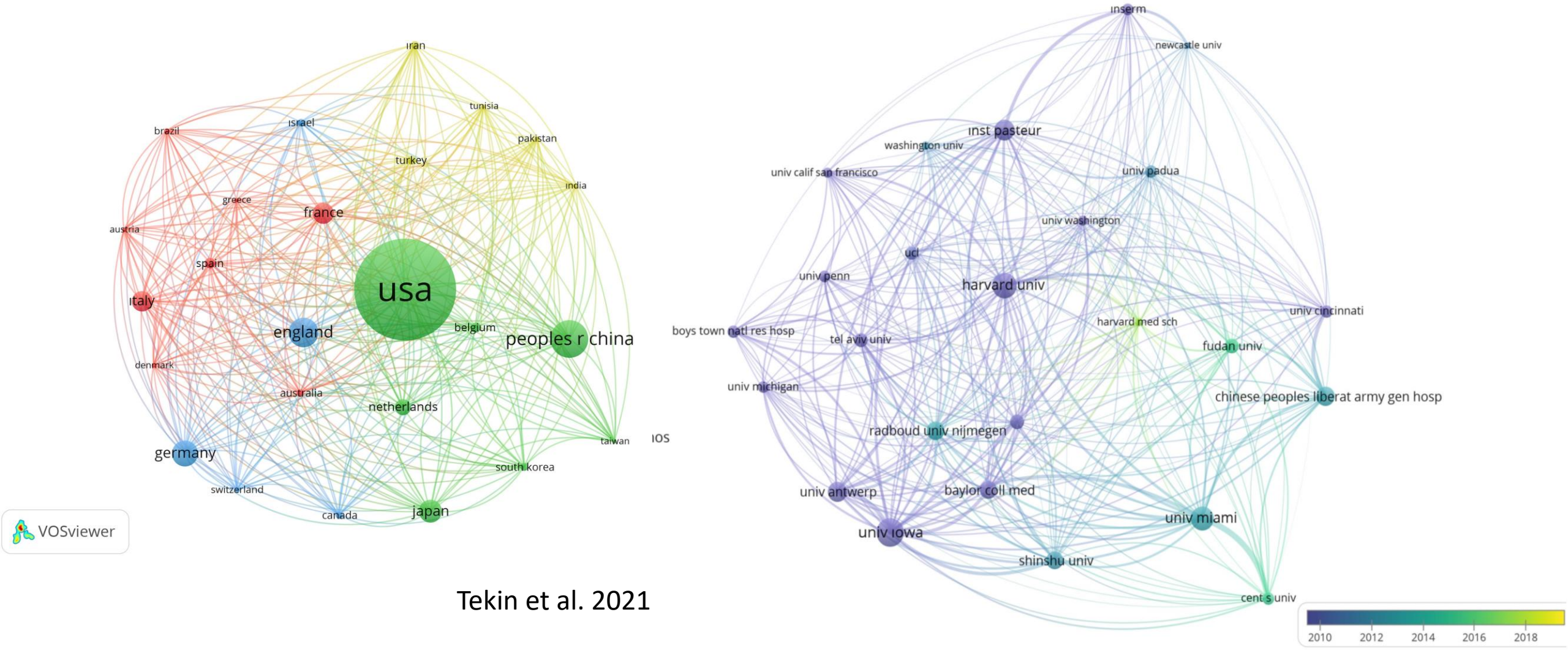
Potential Pipeline for Genetic HL Testing
NIH-NIDCD R01 DC019642

1. Failed NBHS -> refer for genetic screening
2. Collect patient and parental/family DNA (saliva, blood)
3. Sanger-sequence frequent variants/genes (*SLC26A4* c.706C>G, *GJB2*)
4. If Sanger(-), perform exome sequencing -> coding variants
5. If exome(-), perform WGS -> non-coding, CNV
6. If WGS(-), keep in databank until new techniques/knowledge are discovered
7. Refer for genetic counseling
8. Also exploring epigenome

Needs: Staff, secure cloud, sequencing

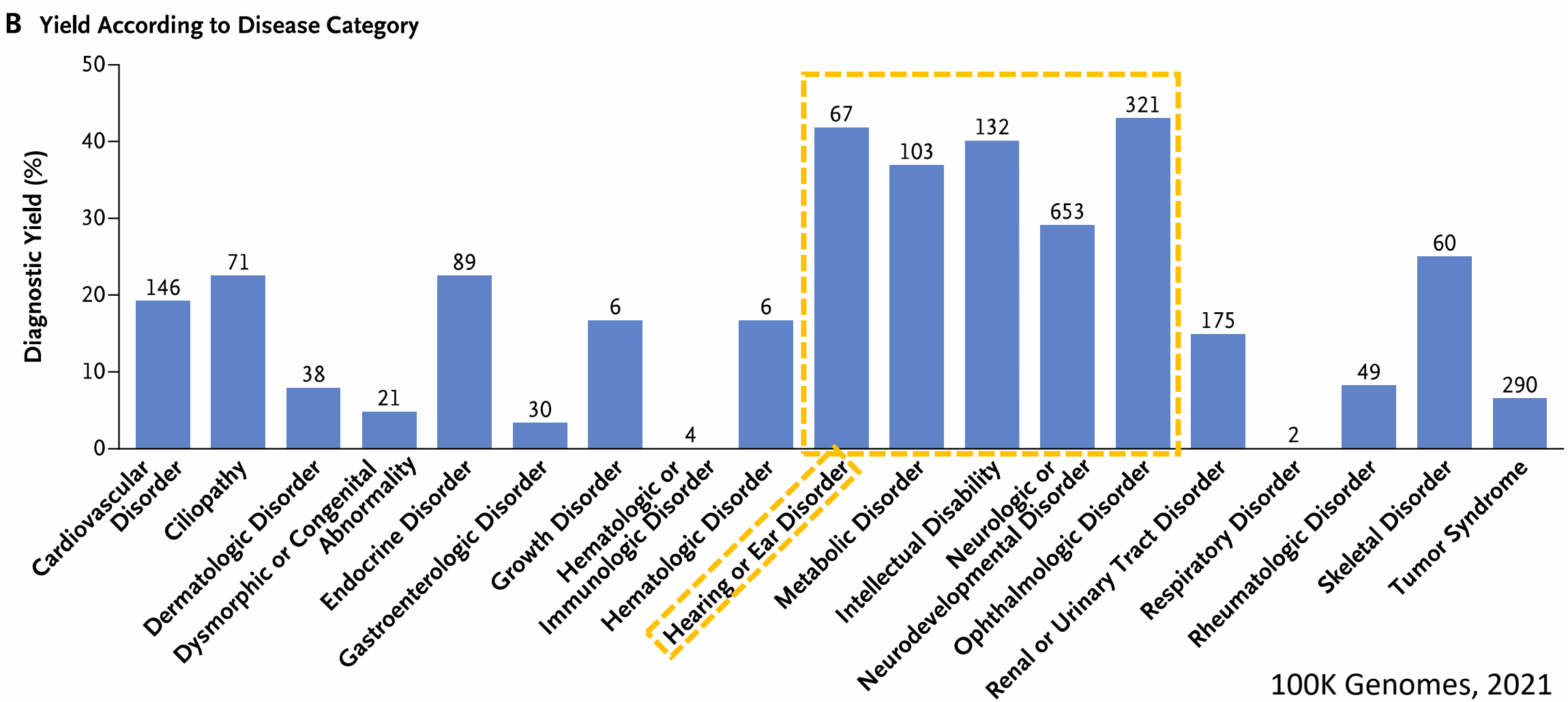
PGC
PHILIPPINE GENOME CENTER

Top Players in Genetic Screening for Hearing Loss



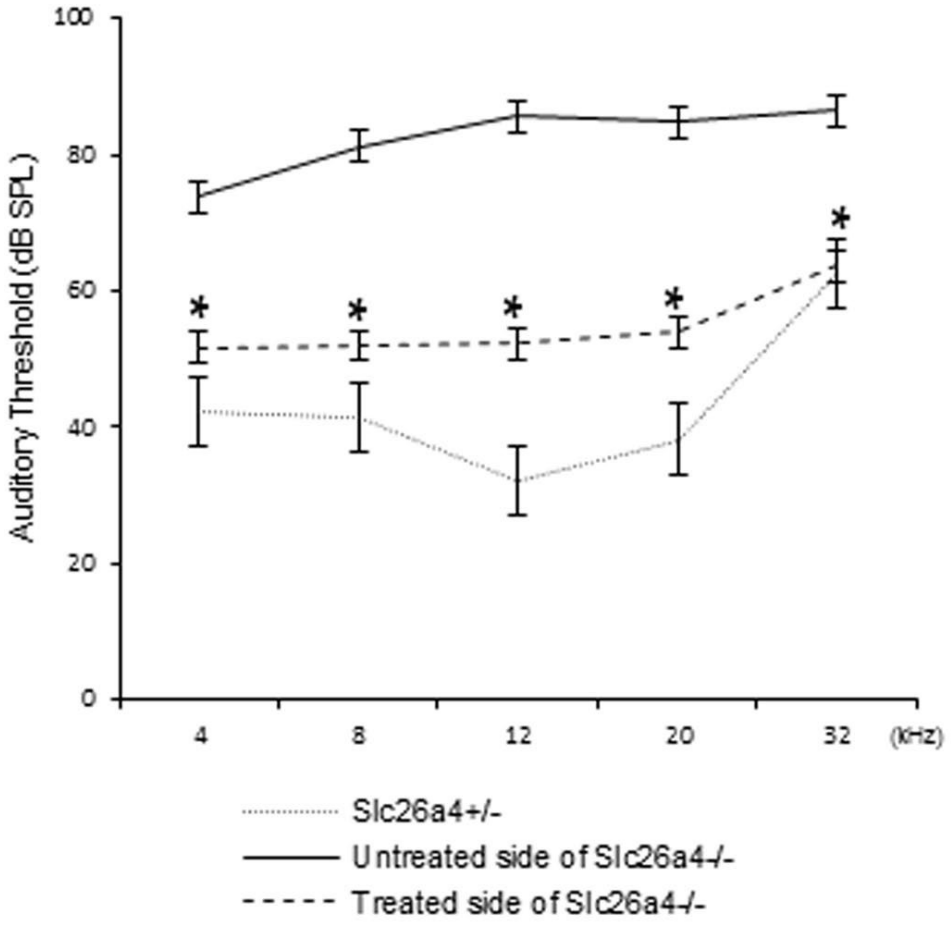
Tekin et al. 2021

A. Hearing Loss in Clinical Exome Sequencing or WGS for Rare Diseases

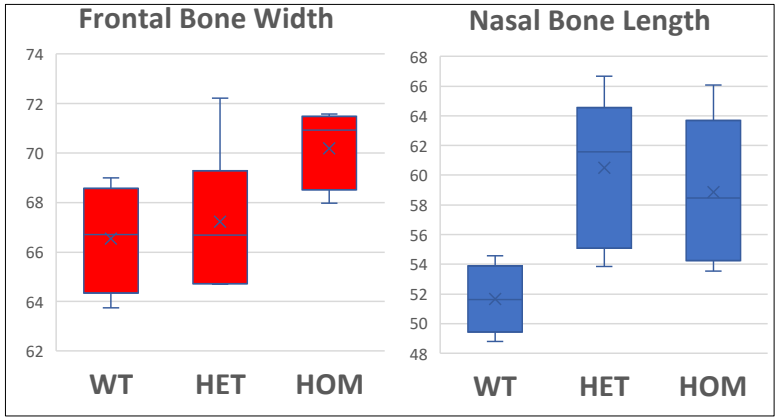


100K Genomes, 2021

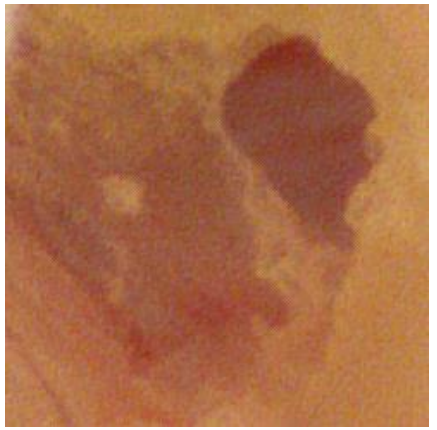
B. Gene-Based Therapy for Filipino Variants



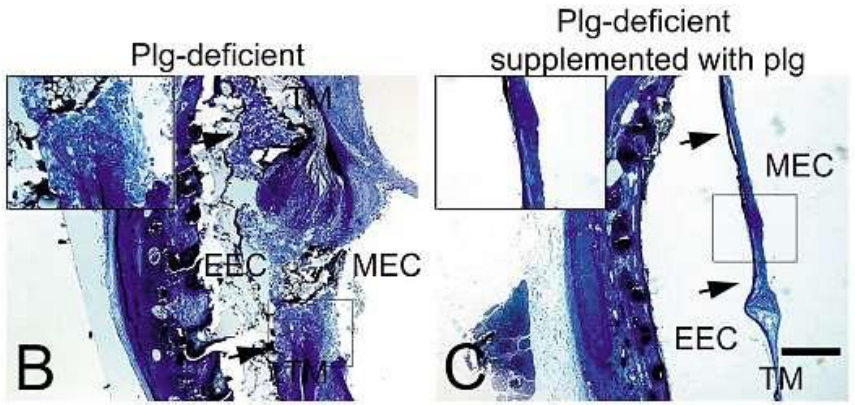
Takeda et al. 2019



A2ml1-KO mice have flatter skulls dorso-ventrally, like the blunted faces of *A2ML1*-mutant zebrafish (Vissers et al. 2015).

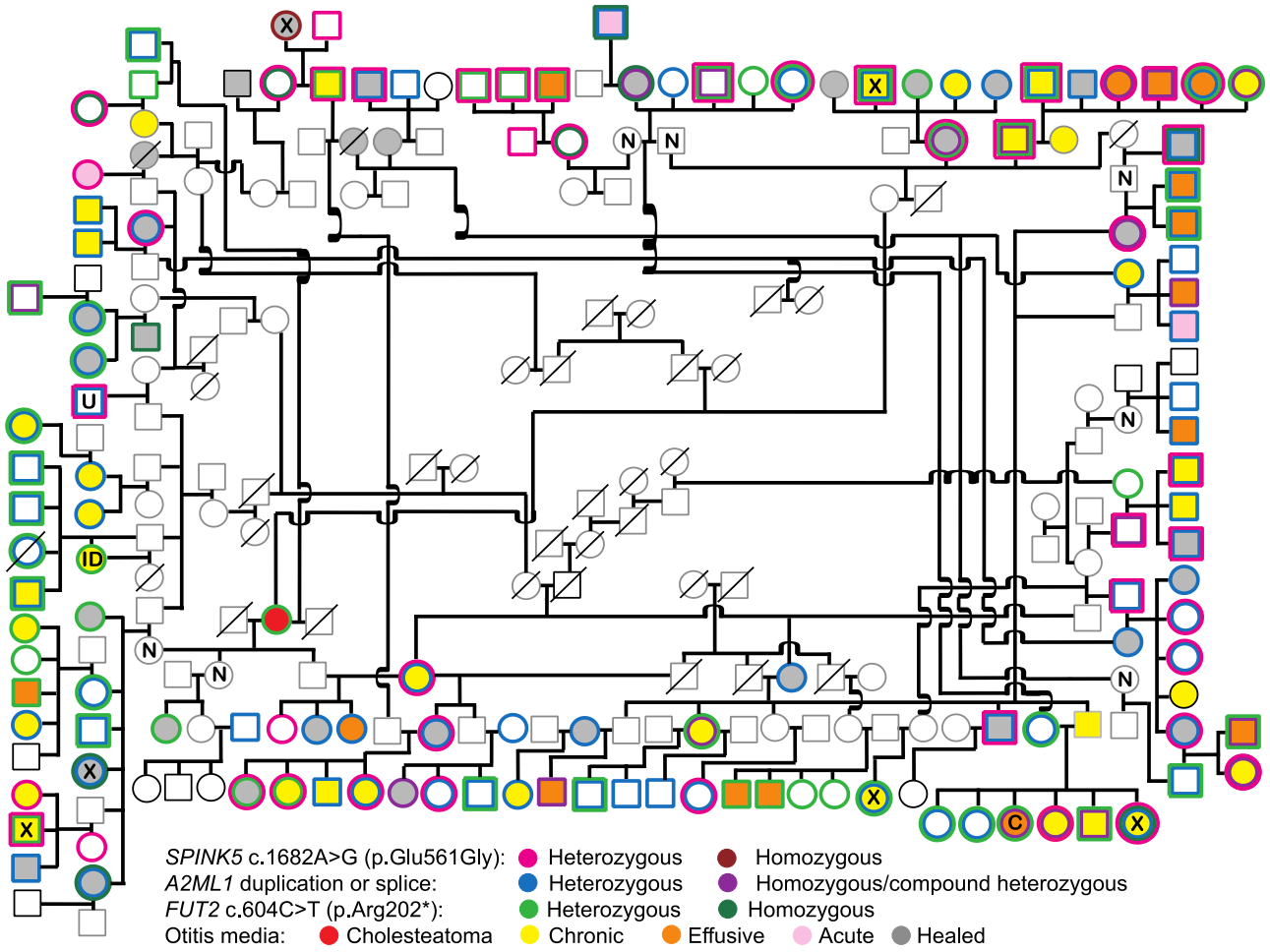


Male *A2ml1+/-* mouse



Li et al. 2006

A2ML1, SPINK5 and *FUT2:* Multiple variants leading to otitis media



Only genetic variants and gingivitis were associated with otitis media in this indigenous population

Services provided to indigenous community

- Follow-up of otologic diagnoses
- Audiologic screening
- Genetic counseling
- Education on prevention
  - Aural hygiene
  - Oral hygiene
  - Pneumococcal vaccination
- Guided antibiotic selection
- No surgical intervention so far

Conclusions

- Filipino studies on congenital hearing loss can aid in clinical practice and scientific development
- Currently doable, will need to train technical staff
- Costs will be driven by volume and staff salaries
- Validity studies for genetic and infection screening are essential
- Developing gene-based therapies need to be tailored to population

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- CM Chiong
- MRT Reyes-Quintos
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- EM Cutiongco-de la Paz

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