Genetics of Pediatric Hearing Loss

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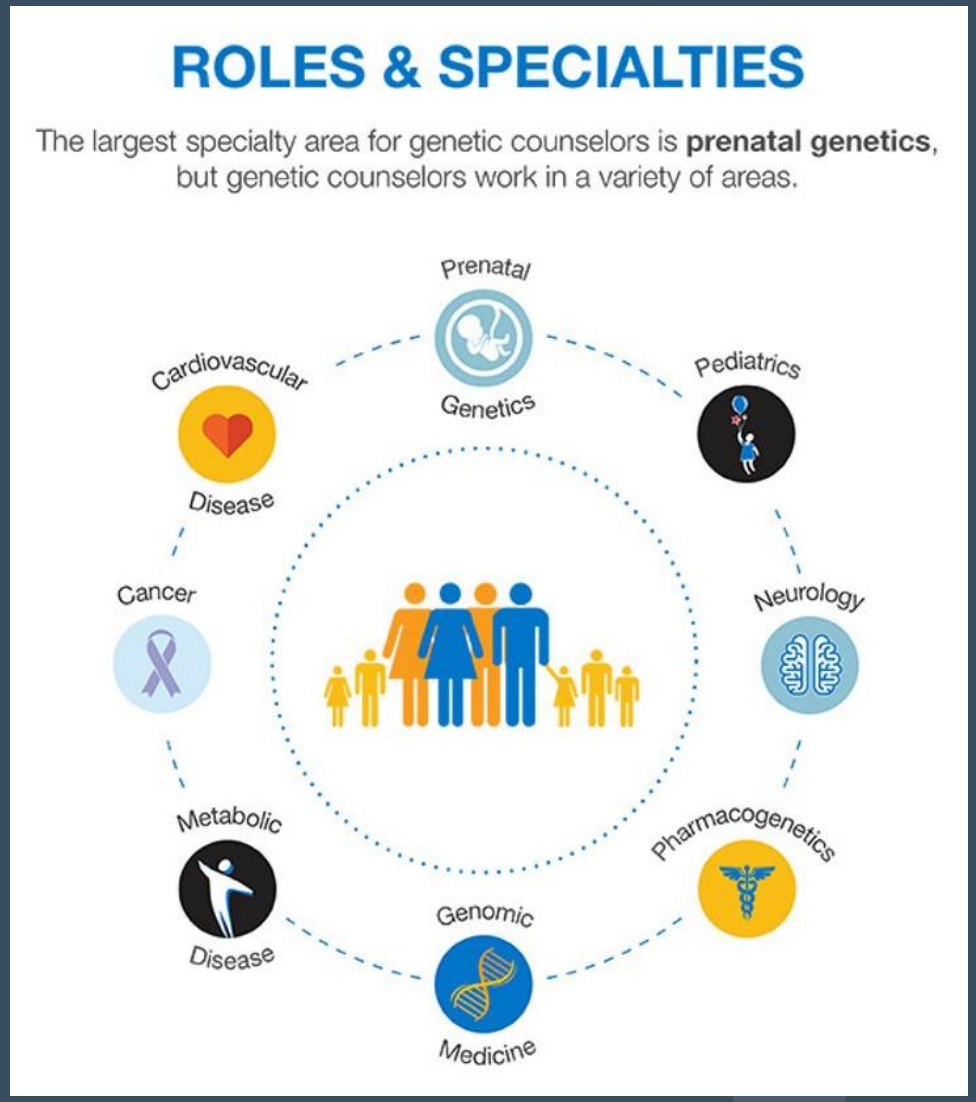
Outline

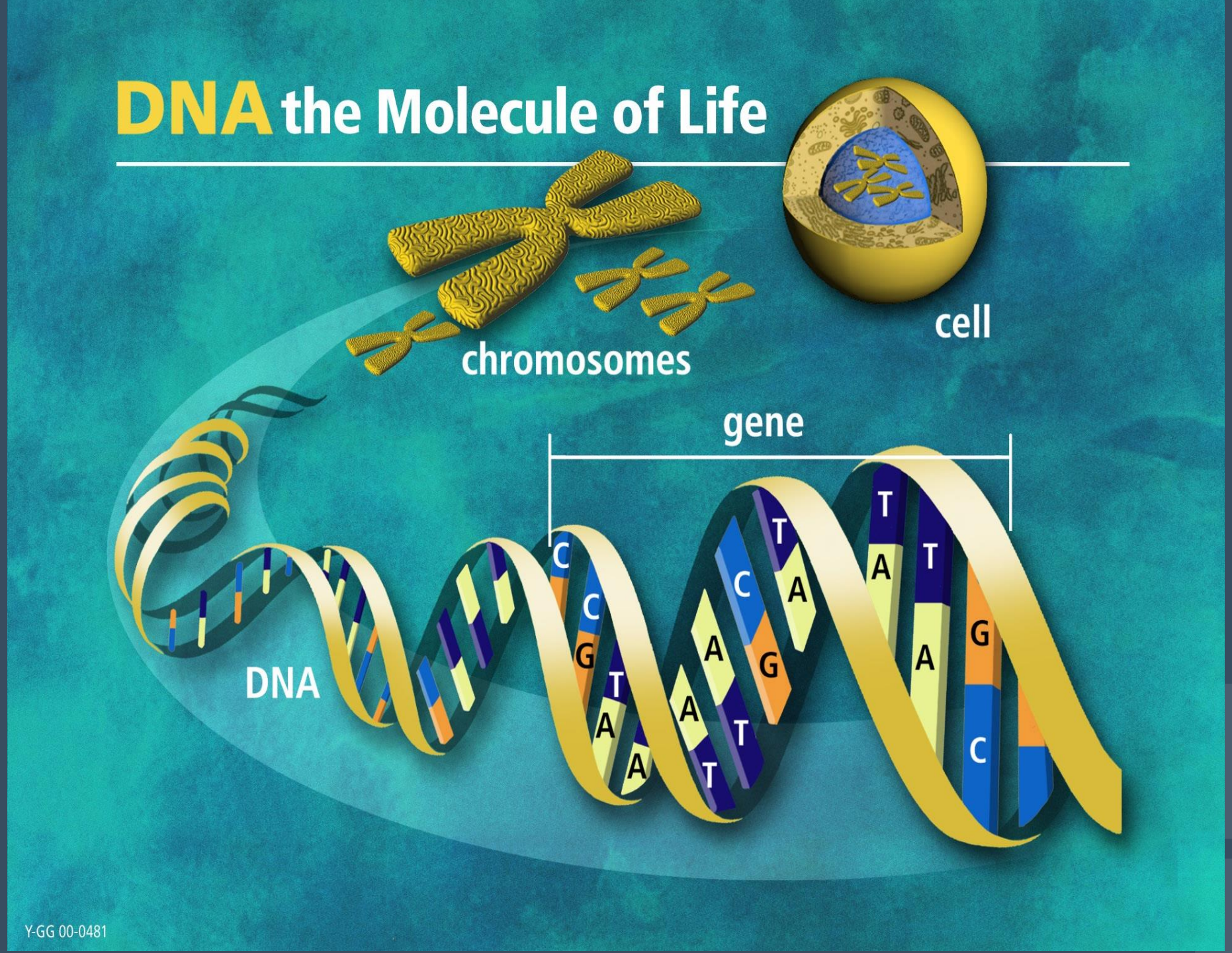
- Genetic Counseling
- Genetics Overview
- Genetics evaluation and testing
  - Clinic Structures
- Nonsyndromic hearing loss
- Syndromic hearing loss
- Case Examples

- *Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process involves:*
  - *Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.*
  - *Education about inheritance, testing, management, prevention, resources and research.*
  - *Counseling to promote informed choices and adaptation to the risk or condition (NSGC, 2006)*

Genetic Counseling Overview

- More than 5000 genetic counselors in the country
  - In various specialties (cancer, prenatal, pediatrics, cardiovascular, etc…)
- Attend 2 year master's program with coursework in genetics, research, and clinical rotations




DNA the Molecule of Life
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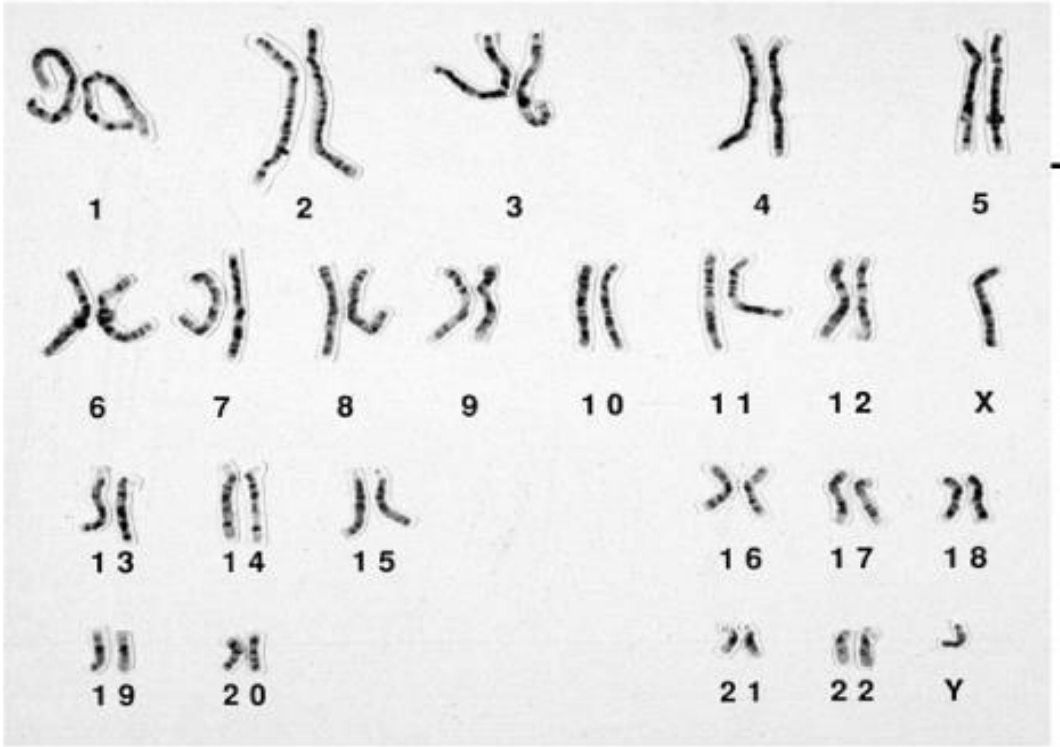
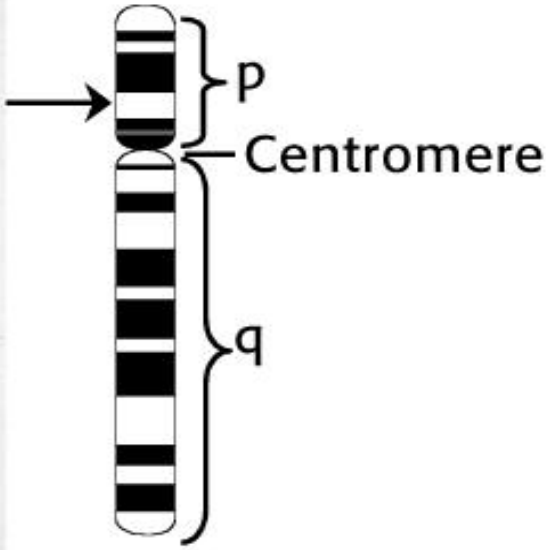
Normal Male Karyotype





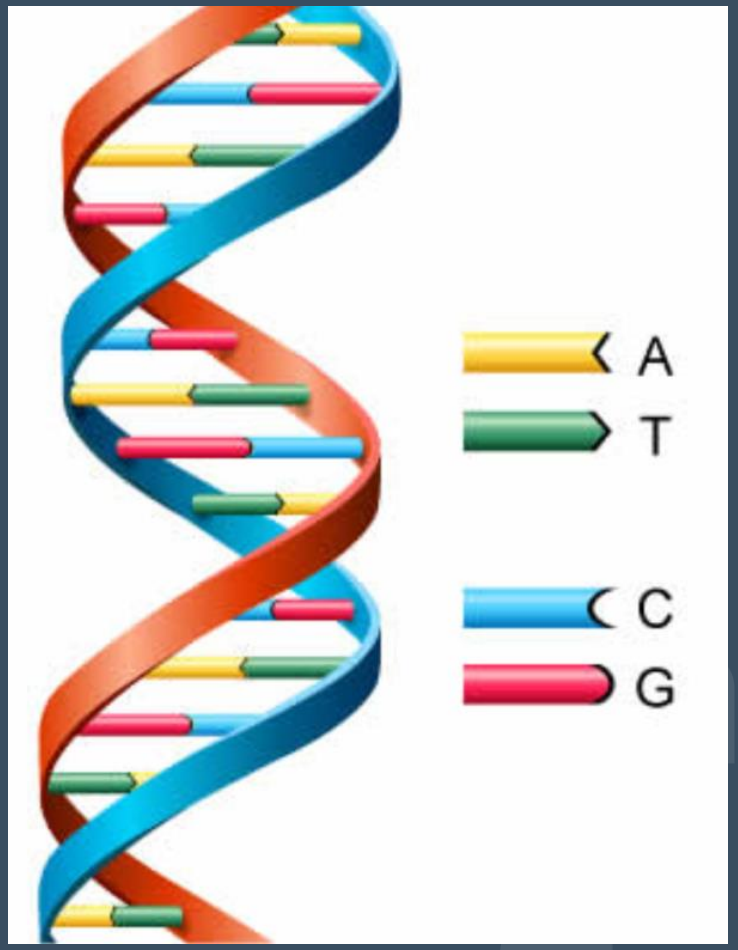
Chromosome 5

Karyotype courtesy of Diane Roulston, PhD.

ASCO

Types of Genetic Testing

- Karyotype
- Microarray
- Single gene
- Panels
- Exome sequencing
- Genome sequencing



Genetic Evaluation

- Review medical history
  - Onset and type of hearing loss
  - Other medical concerns, including heart, kidneys, etc.
  - Previous evaluations (CT, MRI, EKG, ophthalmology)
- Family history and risk counseling
- Physical exam for syndromic features when appropriate
- Education on condition and genetic testing options

ACMG Guidelines Support Genetics Eval:

- Goal to identify etiologic diagnosis
  - Individualized health maintenance strategy
  - Identifies unrecognized syndromic HL condition
    - Allows early management of associated medical concerns
  - Accurate genetic counseling for the family
- 95% of newborns with HL identified by NBHS are born to hearing parents

Li, MM et al. 2022. ACMG Practice Resource: Clinical Evaluation and etiologic Diagnosis of Hearing Loss: A Clinical Practice Resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine* 1-15. doi: https://doi.org/10.1016/j.gim.2022.03.018

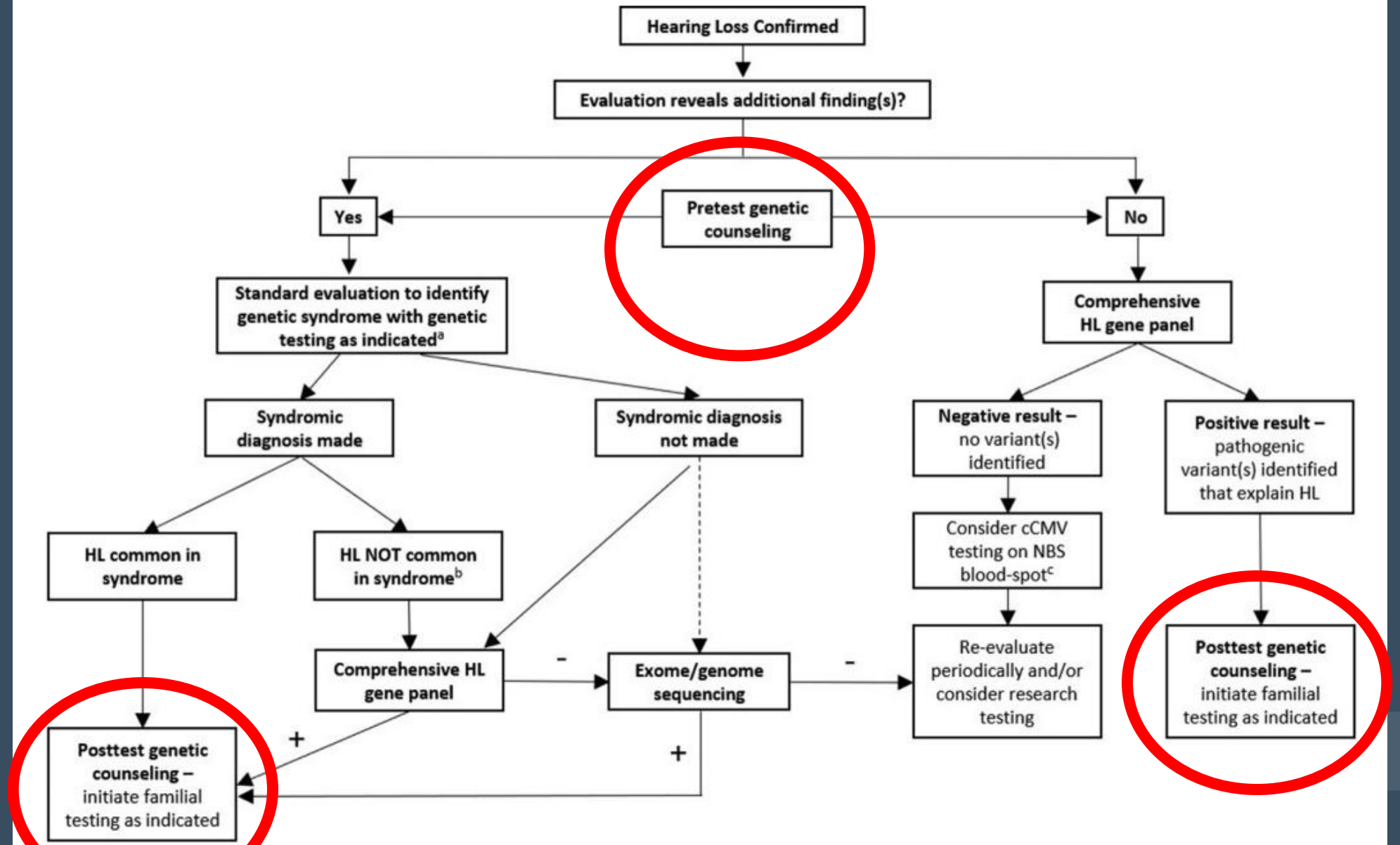


Figure 1 Approach to clinical and diagnostic evaluation for hearing loss. [a]Genetic testing could include single-gene tests, multigene panels, chromosome analysis, or microarray depending on clinical findings. [b]If genetic syndrome identified is not typically associated with HL, proceed to evaluate for secondary cause of HL. [c]Birth state may screen newborns for cCMV. The symbol + indicates positive. The symbol – indicates negative. cCMV, congenital cytomegalovirus; HL, hearing loss; NBS, newborn screening.

Li, et al. 2022.

Pre test and Post test counseling

- Appropriate tests available including insurance/billings options and process
- Types of results (pathogenic/positive, negative, VUS)
- Implications for family members
- Informed consent
- Results review including variant, condition associated, inheritance
    - Next steps if nondiagnostic
- Any management recommendations
- Available resources (support and/or educational)
- Implications for family members (follow-up testing, screenings, etc)

Basic Elements of Informed Consent for Genetic Testing

1. Competence
2. Amount and accuracy of information
3. Patient's understanding
4. Voluntariness
5. Authorization

1. Information on the specific test being performed
2. Implications of a positive, VUS, and negative result
3. Possibility that the test will not be informative
4. Options for risk estimation without genetic testing
5. Risk of passing pathogenic variant to children
6. Accuracy of test
7. Fees involved in testing and counseling
8. Psychological implications of test results (benefits and risks)
9. Risks of insurance or employer discrimination
10. Confidentiality issues
11. Options/limitations of surveillance and strategies for prevention
12. Importance of sharing genetic test results with at-risk relatives

Schmerler S. (2009). Ethical and Legal Issues. In W.R. Uhlmann, J.L. Schuette, B.M. Yashar (Eds.), A guide to genetic counseling 2nd edition (370-371). New Jersey: John Wiley & Sons Inc.

ASCO Policy Statement on Genetic Testing for Cancer Susceptability J Clin Onc 2003;21:2397-2406

What protections are in place?

- Health Insurance Portability and Accountability Act (HIPAA)
- Genetic Information Nondiscrimination Act
  - GINAhelp.org
  - GINA is Civil Rights Legislation affecting employment and health insurability

***Genetic information means family history, up to 4th degree relatives, utilization of genetic services, participation in genetic research, and genetic testing, including results.

Genetic Information Nondiscrimination Act (GINA)

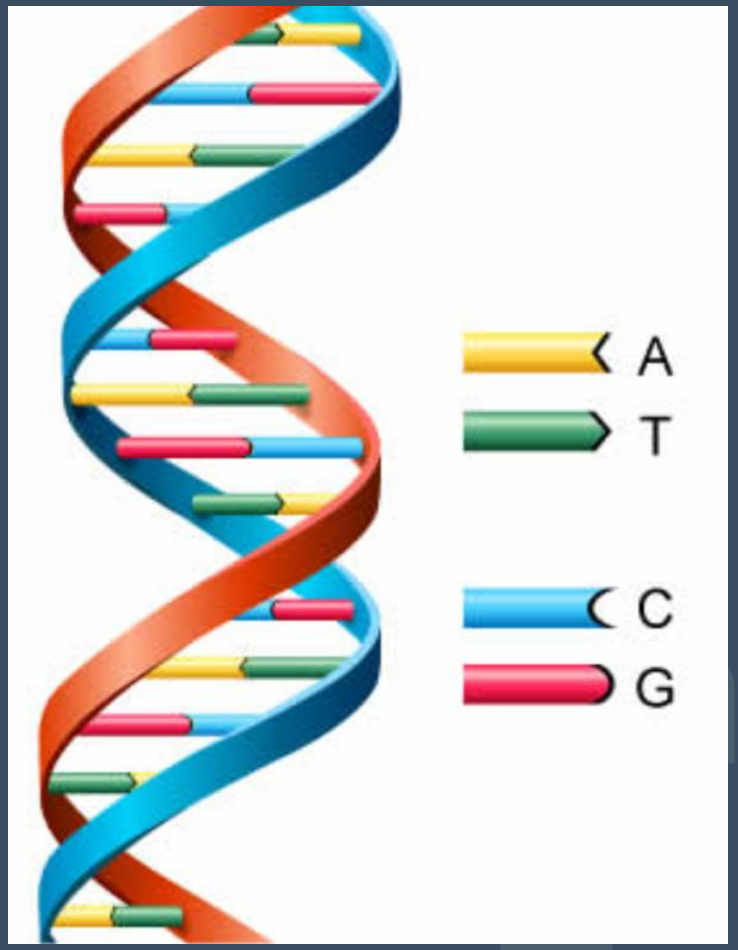
- GINA does not…
  - Apply to patients who have a *current* diagnosis of any disease -- it applies to predictive genetic information
  - Mandate coverage of any particular medical test or treatment
  - Offer protection for life or disability insurance or employees of the military

Importance of consenting

- Addressing concerns up front (insurance coverage and/or discrimination are common concerns)
- Preparing patient (and parents) for types of results and what results can mean for them
  - Broad test for diagnosis may identify rare condition with no management recs
  - Panel includes other conditions/health associations
  - Uncertain results that we may not have additional info on for years
- Consenting adults vs. pediatric patients for genetic testing
  - Secondary findings, carrier status, unexpected other health concerns
- Bringing up the possibility of parent/family member testing in results follow-up or consenting for it with exome sequencing and/or family variant testing
  - Nonpaternity, egg or sperm donor used, consanguinity, etc…
- Each lab’s test requisition form is different!

Types of Genetic Testing

- Karyotype
- Microarray
- Single gene
- Panels
- Exome sequencing
- Genome sequencing



Considerations for panel testing:

- Lab A – 224 gene hearing loss panel
- Lab B – 205 gene hearing loss panel
- Lab C – 224 gene hearing loss panel
  - 9 mitochondrial genes
- Lab D – 150 gene hearing loss panel
  - 4 mitochondrial genes

Different labs have different options for family follow-up variant testing (cost to lab vs patient, only path variants covered vs VUS also, etc)

All have different insurance billing practices (institutional vs 3rd party, financial assistance plans, self pay prices etc…

Each lab has different practices regarding interpretation processes (review board for each test, automated processes, etc…)

Variants of Uncertain Significance

- “VUS should not be used in clinical decision-making”
  - Falls between benign/likely benign and likely pathogenic/pathogenic
  - “Additional monitoring of the patient may be prudent”
- VUS is NOT a diagnostic result
  - They may be reclassified in the future
  - Rarely clinical genetics will reinterpret a VUS as diagnostic if clinical phenotype and genotype align without other possible diagnoses
  - ~80% of VUS that are reclassified are reclassified to benign or likely benign*
- VUS often require follow-up testing of parents or other affected family members
  - Sometimes follow-up testing is not recommended or not informative
  - Sometimes not possible due to costs, location of family members, complex social relationships, etc
- Variants can be reviewed in ClinVar to evaluate other labs interpretation

ACMG Guidelines: *Genetics in Medicine* (2015) 17(5): 405-424: doi:10.1038/gim.2015.30
**Genetics in Medicine* (2019) 21:1435-1442; https://doi.org/10.1038/s41436-018-0335-7

Sponsored testing

- Many labs now offer sponsored tests for specific conditions, when a pharmaceutical company or research organization covers the cost of testing
  - Most HL sponsored panels are for ANSD
- **Sponsored testing DOES NOT EQUAL free testing**
- Each sponsored test has an agreement with a specific company without explicit guidance on how a patient's information might be used/shared
- Some sponsored tests allow patient re-contact to participate in further research
  - Need to look into what is provided and explain this to patients
  - Not always the most comprehensive option – some only offer partial panels
- Need to properly document that sponsored and non-sponsored options were offered and consented for legal purposes

Genetics Evaluation - Benefits

- Facilitates establishing etiologic diagnosis
- Provides information on prognosis
- Essential for accurate genetic counseling
- May avoid other costly and time-consuming medical tests
- Helpful for individualized management and identification of syndromic causes
- Psychosocial support for parents and patient
- Complete Fhx=identifying other red flags for genetic conditions

Genetics Evaluation - Limitations

- Limited change to medical management if nonsyndromic HL
- Frequent inability to determine a diagnosis
- Insurance denials and/or costs (high deductibles, etc)
- Still learning….

Gene Therapy:

April 2018 | Bonus Feature

First Ge… Retinal…

COVER …

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ClinicalTrials.gov

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Trial record **3 of 3** for: auditory neuropathy

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Otoferlin Gene-Mediated Hearing Loss Natural History Study

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our

ClinicalTrials.gov Identifier: NCT…572073

Recruitment Status : Recruiting
First Posted : October 7, 2022
Last Update Posted : October 7, 2022

See Contacts and Locations

…14,15,16

…s study

…Study to Evaluat… (Sirius)

…e OTOF Gene

ClinicalTrials.gov Identifier: NCT05158296

Genetics Evaluations Clinics

- Hearing Loss genetics clinics
  - GC only or GC/MD
- General Genetics clinics
- Multidisciplinary clinics

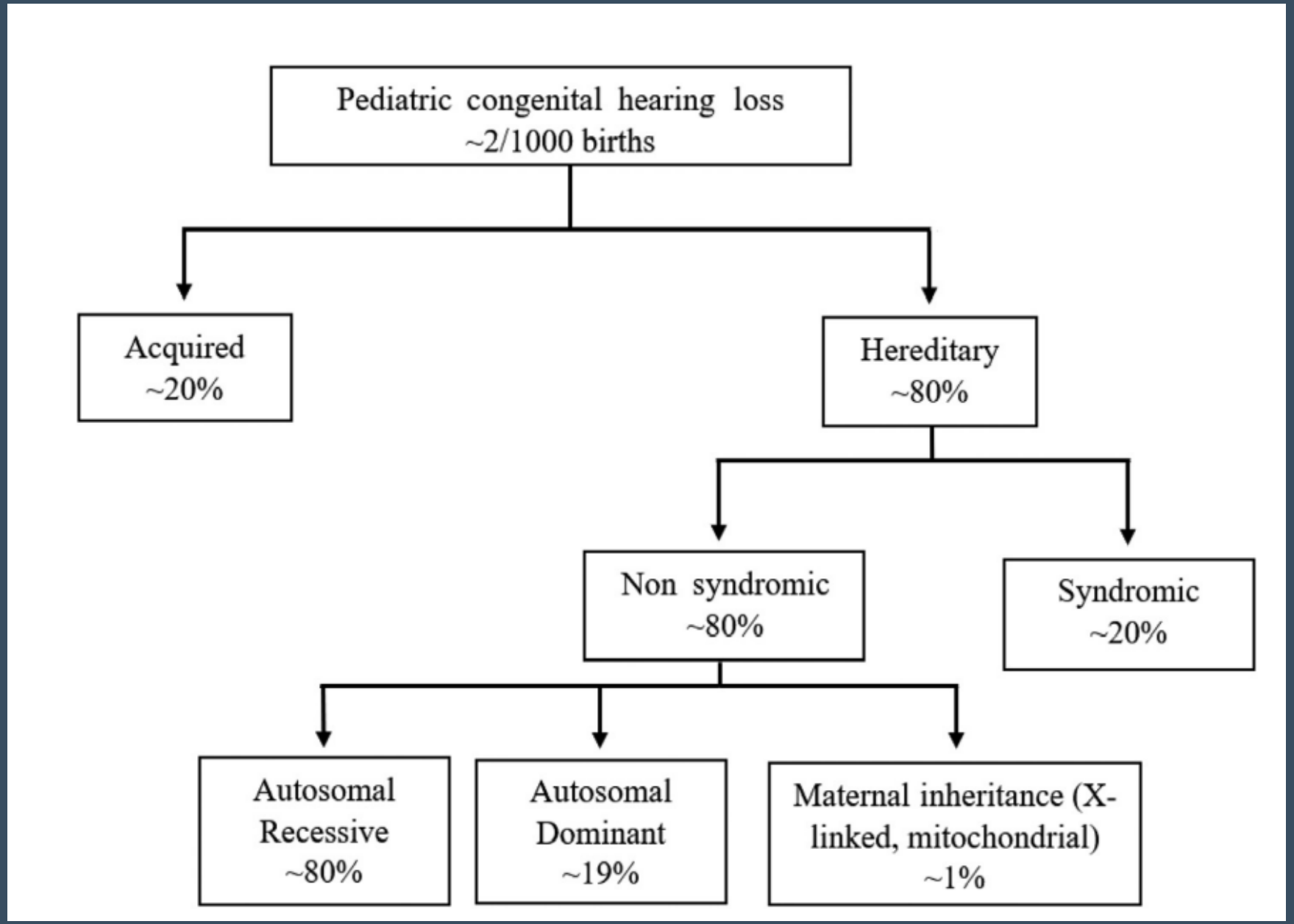
Pediatric Hearing Loss Management Clinic (PHMC)

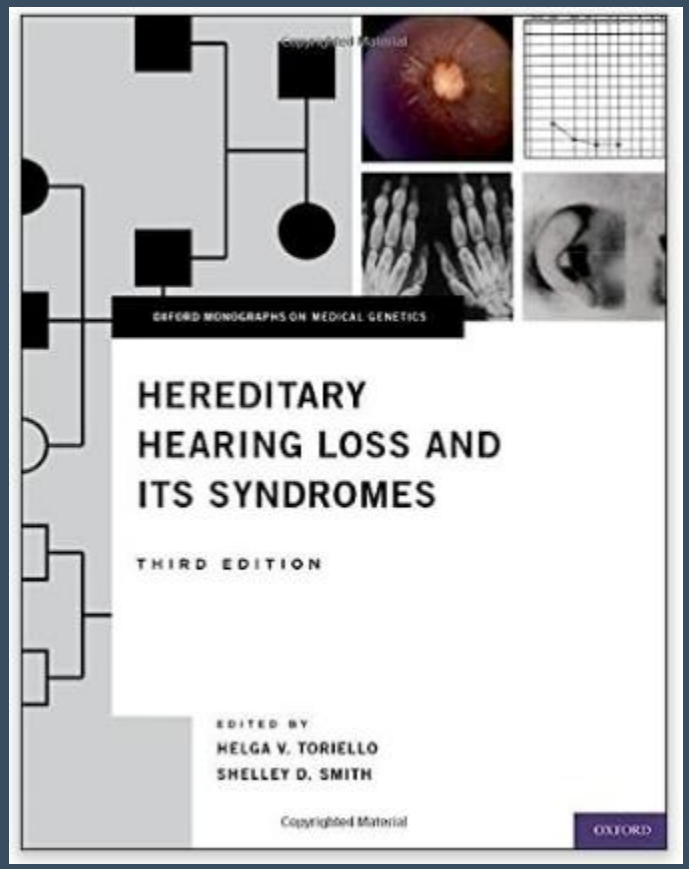
Medical: Samantha Anne, MD
Audiology: Carmen Jamis, AuD, CCC/A
Genetics: Sarah Mazzola, MS, CGC
Speech-Language Pathology: Donald M Goldberg, PhD, CCC/A-SLP; LSLS
Administrative Assistant: Alexia Chesbrough
Nursing Staff: Alysia Pleban, RN, BSN

Cleveland Clinic

Additional workup includes EKG, MRI/CT, CMV, ophthy referral

Recommend genetic testing in bilateral or unilateral+ HL (Fhx, imaging, other health issues)





Li et al., 2022 quotes 30% is syndromic

GeneReviews https://www.ncbi.nlm.nih.gov/books/NBK1434/

Shave S, Botti C, Kwong K. *Congenital Sensorineural Hearing Loss.* Pediatr Clin N Am 69 (2022) 221–234 https://doi.org/10.1016/j.pcl.2021.12.006

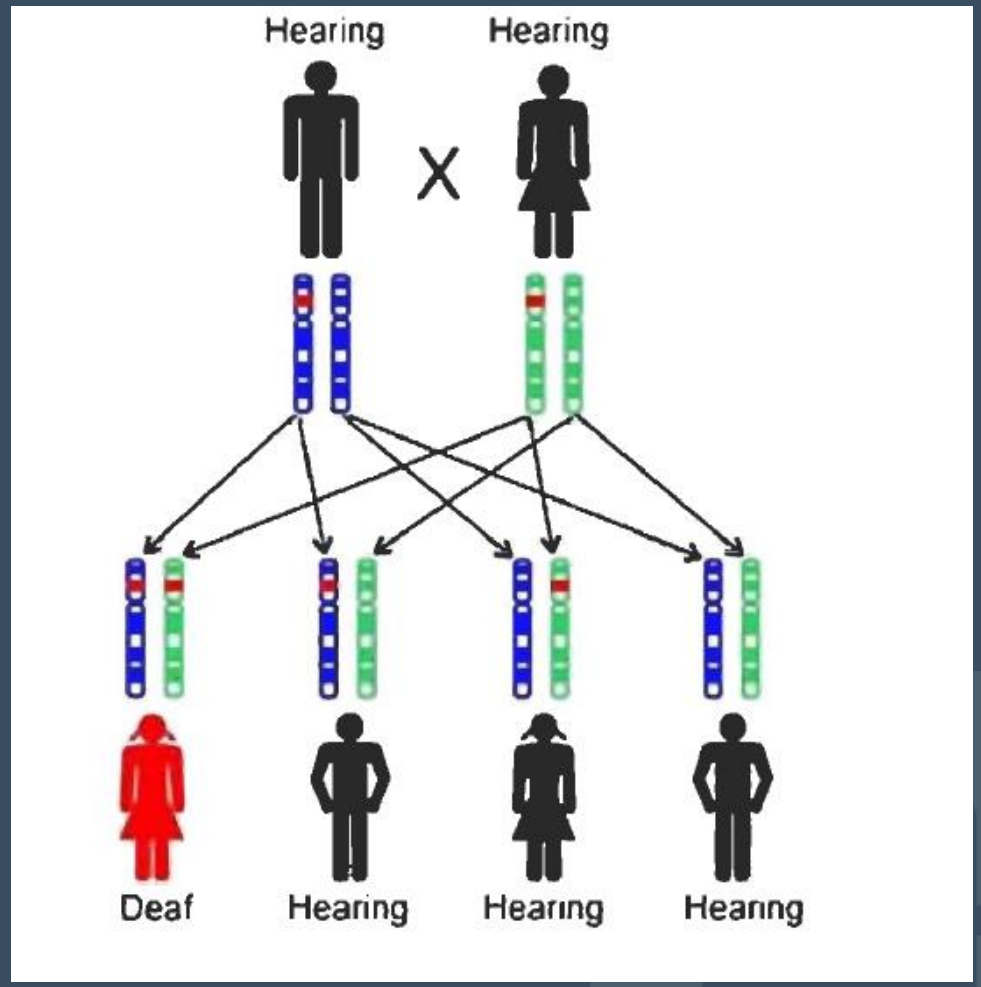
Autosomal Recessive Nonsyndromic Hearing Loss

- Congenital severe to profound type is most common
- ~50% of AR nonsyndromic hearing loss is due to Connexin (DFNB1)

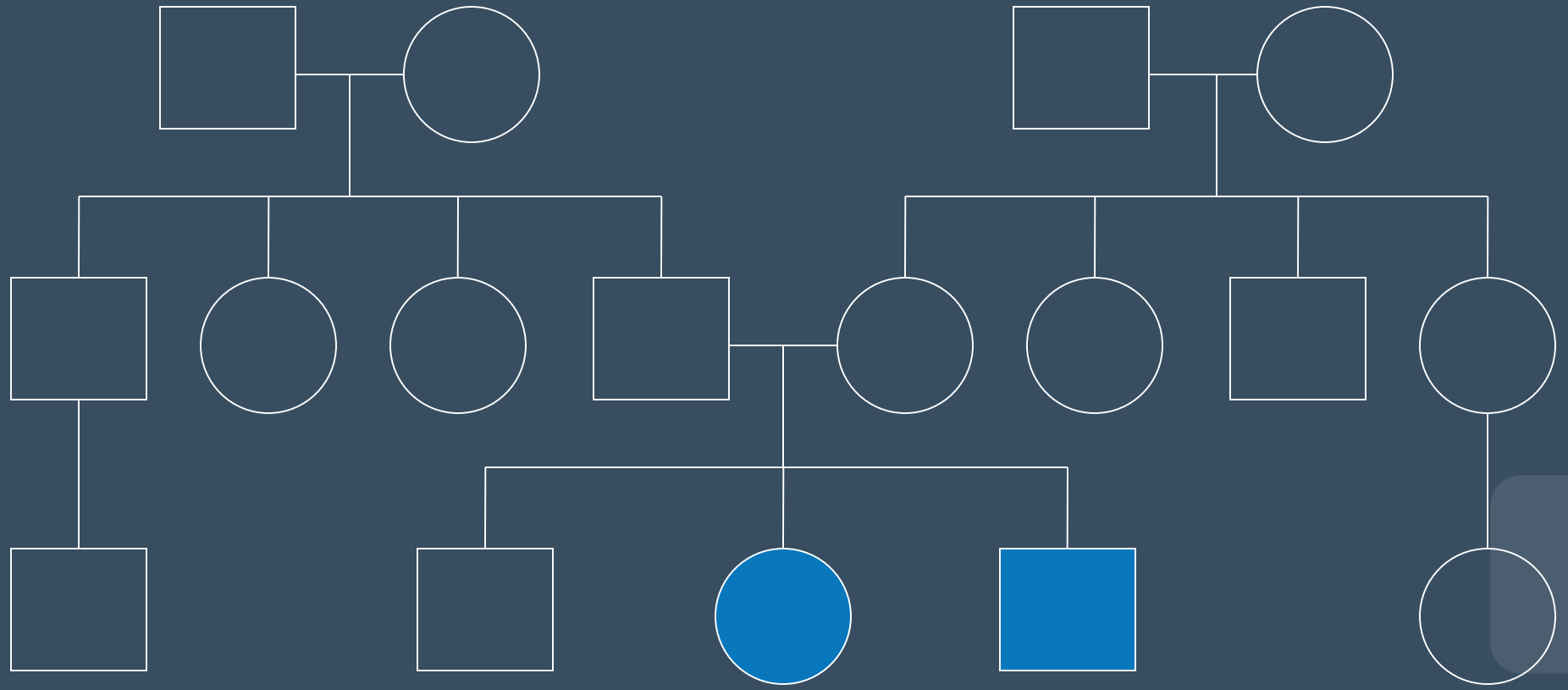
DFNB1 → Connexin 26 (protein name)

↓

GJB2 (gap junction β 2) (gene name)



Autosomal Recessive



GJB2 (Connexin 26)

- Autosomal recessive (most pathogenic variants)
- 99% are homozygotes or compound heterozygotes for pathogenic variants in *GJB2*
    - Carrier frequency in US is ~ 2-4%
- 1% have 1 pathogenic variant in *GJB2* & deletion of upstream regulatory elements & part of *GJB6* (Connexin 30)
- Most common pathogenic variant: c.35delG
    - Causes frameshift, premature stop codon
- DFNA3 – Autosomal dominant: progressive, moderate-to-severe SNHL – caused by certain heterozygous mutations of *GJB2* or (less common) *GJB6*

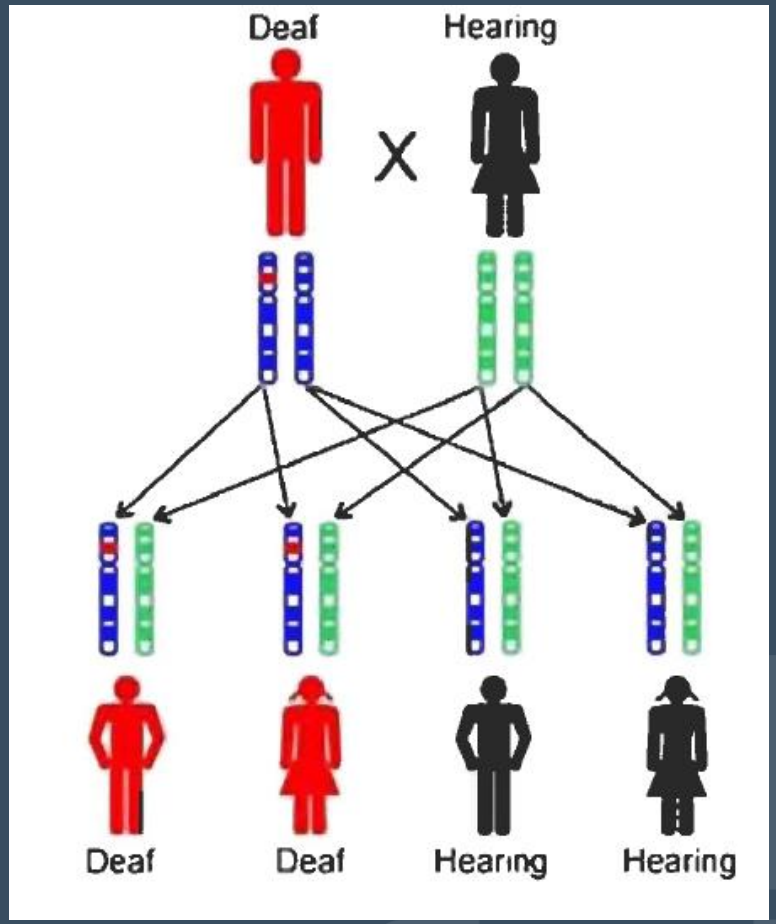
STRC

- Next most common AR nonsyndromic HL
- ~30% of patients with mild to moderate HL
- Most variants large copy number variants (CNV)
  - Biallelic *CATSPER2-STRC* deletions cause male infertility + HL
    - Females HL only

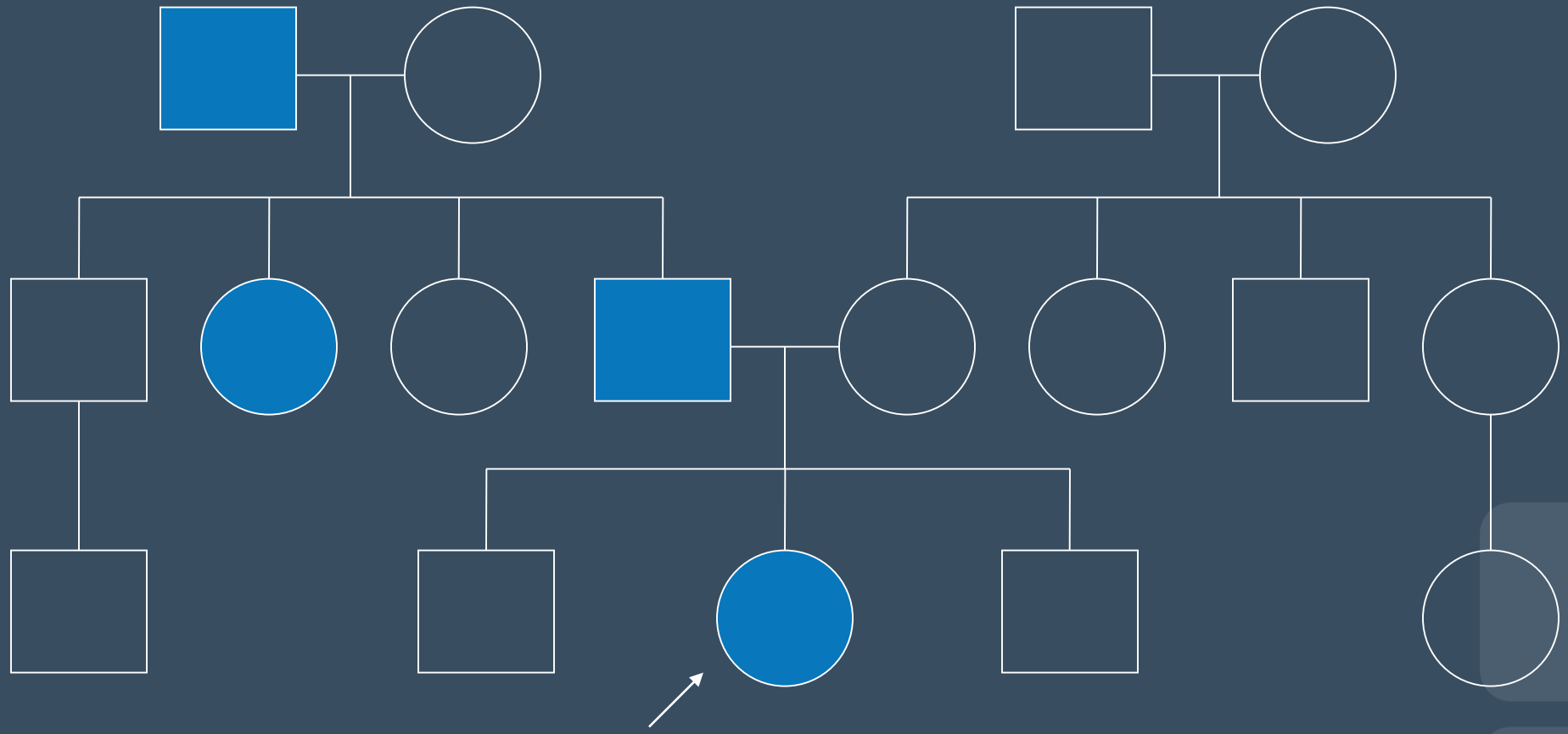
Autosomal Dominant Nonsyndromic Hearing Loss

- Accounts for ~15-20% of cases of nonsyndromic HL
- Frequently onset is postlingual and is progressive
  - Genetic testing diagnostic yield for adult-onset HL is between 18-35%
- Some forms also include vestibular dysfunction Li et al., 2022
- Over 50 genes have been identified
- Many found in only one or two families
- Testing is complicated, with multigene panels now on the market

Difficult to diagnosis without a family history



Autosomal Dominant



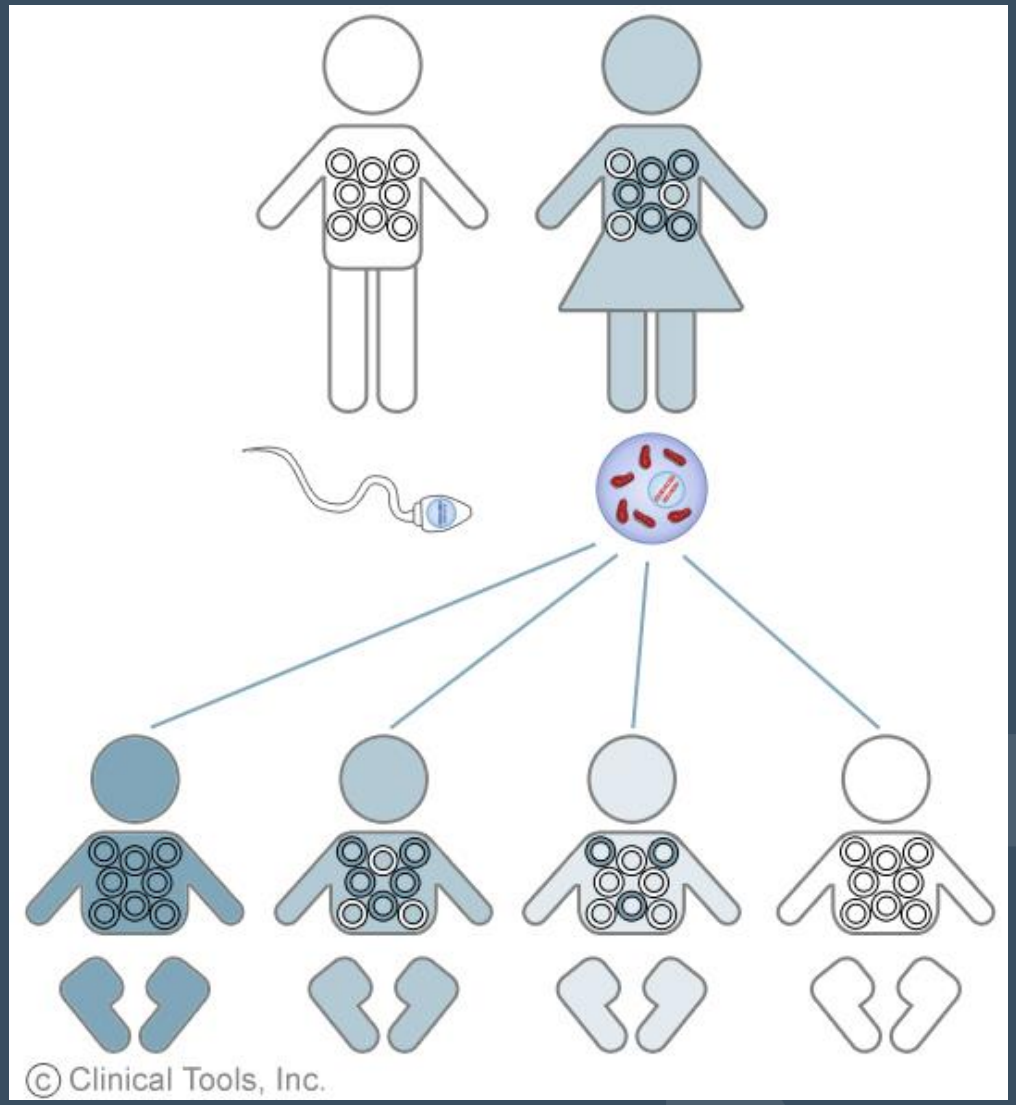
Mitochondrial

Mitochondrial genome:

- Variety of metabolic functions
- Transmitted from mother to child
  - Heteroplasmy levels

Non syndromic Mitochondrial HL:

- Moderate to profound HL common



Mitochondrial Nonsyndromic HL

Typically moderate to profound HL

MT-RNR1 gene

- Predisposition to amnioglycoside ototoxicity and/or late-onset HL
- Common variants: m.1555A>G, m.1494C>T

MT-TS1 gene

- Childhood onset of sensorineural HL
- Common variants: m.7445A>G, m.7510T>C, m.7511T>C
- Some variants also cause palmoplantar keratoderma

MT-RNR1 Variants

- HL is related to administration of amnioglycosides (eg. gentamycin, tobramycin, streptomycin, etc.)
  - May only require one dose
  - “Dose-related” amnioglycoside induced HL (ototoxicity) can occur even without MT-RNR1 pathogenic variant
- Penetrance – m.1555A>G pathogenic variant (present in 0.2% of population):
  - History of aminoglycoside therapy
    - Occurs within a few weeks of exposure, permanent
    - Penetrance – virtually 100%
  - No history of aminoglycoside therapy
    - Varies based on level of heteroplasmy
    - Penetrance – 0-65%

Auditory Neuropathy (ANSD)

- *OTOF* and *DFNB59* genes
  - *OTOF* can present as ANSD in early childhood but becomes more consistent with a cochlear defect over time
  - Can also be temperature sensitive, with hearing loss becoming more severe with fever – then resolves
  - *DNFB59* can cause either nonsyndromic hearing loss or ANSD
- ANSD has also been reported with *GJB2* variants
- Can also be seen in syndromes, such as CMT, Friedreich ataxia, mitochondrial disease

https://www.ncbi.nlm.nih.gov/books/NBK1251/

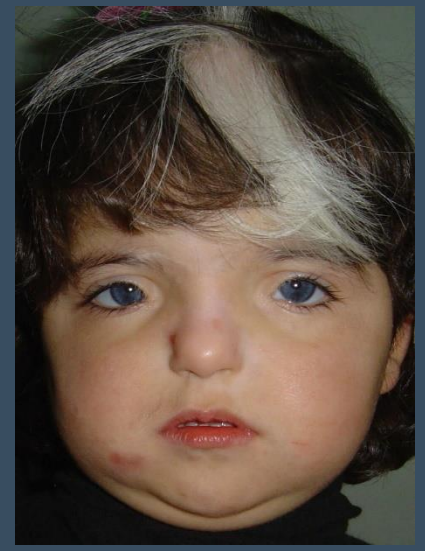
Syndromic HL

- > 400 forms of syndromic deafness have been described
- Is more than one organ system involved?
- Are there similar issues in family members?
- Is there a distinctive or characteristic appearance?

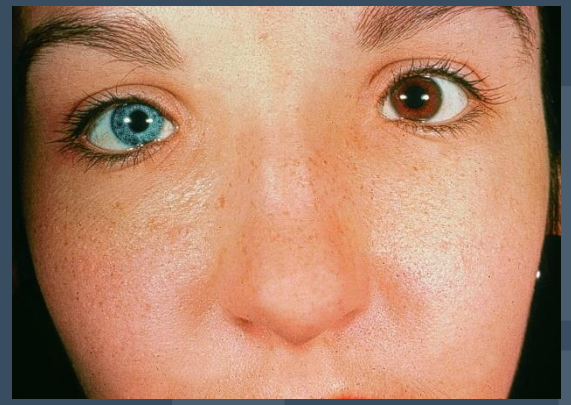
Autosomal Dominant Syndromes

Waardenburg Syndrome

- Accounts for ~3% of childhood hearing impairment
- Incidence is 1 in 4000 live births
- May have unilateral or bilateral SNHL
- Pigmentary features include: white forelock, heterochromia irides, premature graying, and vitiligo
- Craniofacial features include: dystopia canthorum, broad nasal root, and synophrys
- All features are variable in appearance



Lateral displacement of the inner canthi



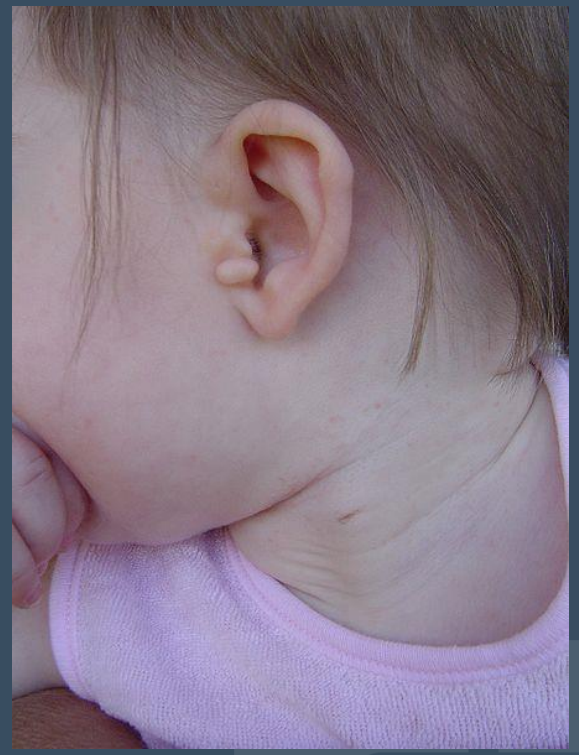
Waardenburg Syndrome

- Four types that are clinically distinguishable
  - Type 1: congenital SNHL (in about 50%), heterochromia irides, white forelock, patchy hypopigmentation, dystopia canthorum
  - Type 2: differentiated by absence of dystopia canthorum, hearing loss in about 75%
  - Type 3: microcephaly, skeletal abnormalities, intellectual disability, in addition to features in type 1
  - Type 4: hearing loss, pigment abnormalities, Hirschsprung disease
- Most are inherited in an autosomal dominant pattern, but may have reduced penetrance

Type	Gene(s)	Proportion/Notes
Type 1	PAX3	> 90%
Type 2	MITF SOX10 SNAI1	10-20% 15% rare
Type 3	PAX3	Can be homozygous
Type 4	SOX10 EDN3 EDNRB	Dominant Recessive Recessive

Branchio-Oto-Renal Spectrum (BOR or BOS)

- Branchial cleft cyst or sinus (50%)
- Oto (ear/hearing)
  - Hearing loss in >90% - sensorineuroal, conductive, or mixed
- Oto
  - Preauricular pits or tags, abnormal pinnae, external canal stenosis or atresia, malformed middle/inner ear
- Renal anomalies (67%)
  - Renal agenesis, hypoplasia, dysplasia



BOR/BOS Genetics

Inheritance: Autosomal dominant

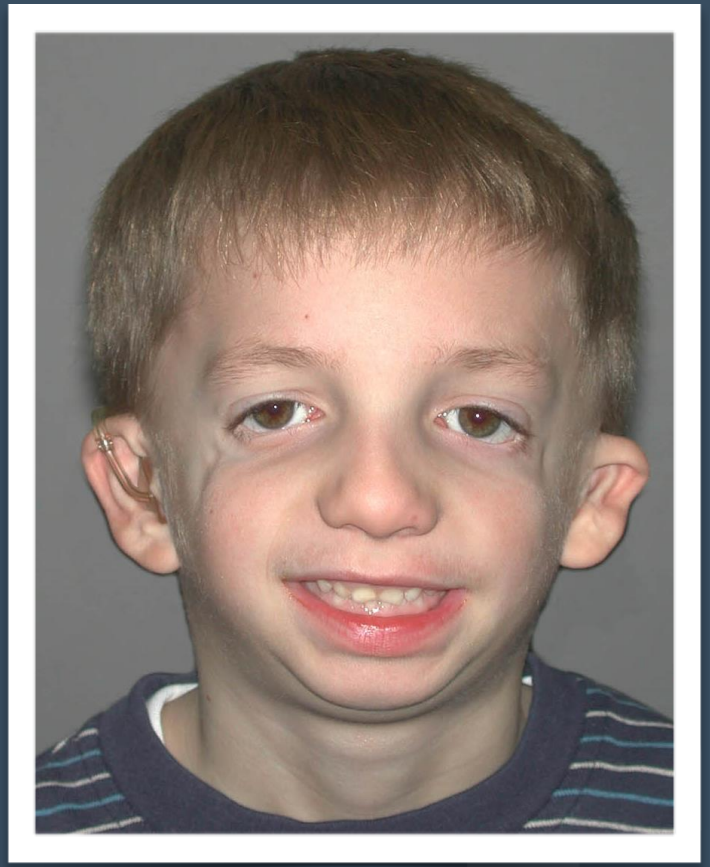
- *EYA1* ~40%
- *SIX5* ~2.5%
- *SIX1* ~2%
- Unknown ~50%

Variable expressivity, 90% have an affected parent

Treacher Collins Syndrome

Clinical features:

- Hypoplasic zygomatic bones & mandible
- Malformed auricles
- Conductive hearing loss
- Ear tags
- Downward slanting palpebral fissures
- Lower lid coloboma; Absent eye lashes
- Macrostomia



Treacher Collins Syndrome

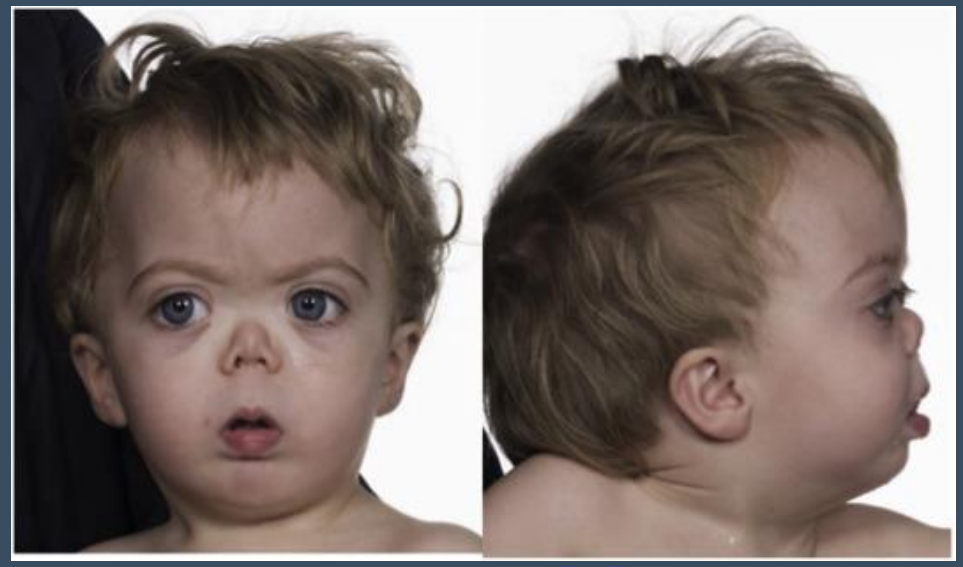
Inheritance: Autosomal dominant

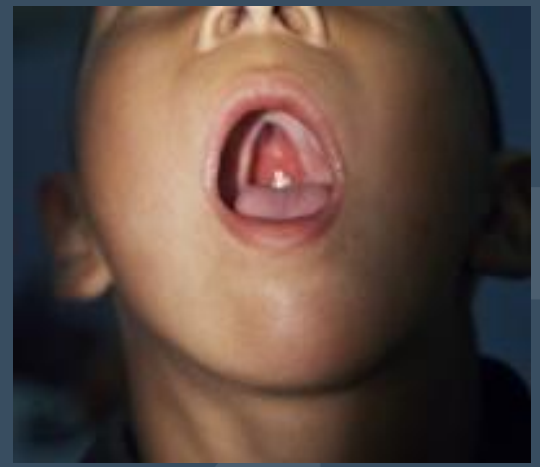
- *TCOF1* – ~ 90%
- *POLR1C* or *POLR1D* – 8%

60% - de novo variant

Stickler Syndrome

- **Craniofacial**
  - Cleft palate & micrognathia (Pierre Robin sequence), malar hypoplasia
- **Eye**
  - Severe myopia, retinal detachment, vitreous abnormalities
- **Skeletal**
  - Short stature, hypermobility, early arthritis, scoliosis
- **SNHL** in about 40%, conductive can also be seen
- Pathogenic variants in one of six collagen genes
  - *COL2A1 (80-90%)*, *COL11A1 (10-20%)*, *COL11A2* – dominant
  - *COL9A1*, *COL9A2*, *COL9A3* - recessive





U-shaped cleft

Neurofibromatosis Type 2

- Affects 1 in 40,000
- Hallmark feature is vestibular schwannoma - tumor on 8th nerve (Also called acoustic neuroma)
- Symptoms include tinnitis, hearing loss, balance problems, occasional facial palsy
- Other features include tumors on brain or spinal cord, early cataracts
- Autosomal dominant pathogenic variants in *NF2* gene
- 50% de novo
- Mosaicism common

Autosomal Recessive Syndromes

Usher Syndrome

- Prevalence of 3.5 per 100,000
  - Accounts for 2-4% of profound hearing loss
- Syndrome characterized by SNHL and retinitis pigmentosa (RP)
- Three subtypes
  - Type 1: congenital bilateral profound HL and abnormal vestibular function
  - Type 2: moderate HL and normal vestibular function
  - Type 3: progressive HL and progressive loss of vestibular function
- Progressive vision loss - night blindness and loss of peripheral vision noted in second decade
  - Electroretinography can identify abnormalities in younger children
- Autosomal recessive, at least 10 different genes

Usher Syndrome

Type	Gene(s)	Proportion
Type 1	MYO7A CDH23 USH1C PCDH15 USH1G CIB2	53-70% 10-20% 6-15% 7-12% Rare Rare
Type 2	USH2A ADGRV1 WHRN	60-80% 6-20% < 10%
Type 3	CLRN1 HARS	

Pendred syndrome

- **Sensorineural HL**
  - Usually profound, but can be variable
  - Usually congenital or rapidly progressive
  - Usually bilateral, can be u/l
- **Malformation of inner ear (~85%)**
  - Mondini malformation and malformations of vestibular canal
  - Most common finding is enlarged vestibular aqueduct (EVA)
  - Both Mondini and EVA are easily recognizable by CT or MRI
- **Euthyroid goiter (~75%)**
  - Usually appears in childhood or early adulthood

Pendred syndrome

Gene: *SLC26A4* – ~90%

Variants in gene can also cause a form of NSHL (DFNB4)

FOXI1 & KCNJ10 – variants account for < 1% each of cases

Digenic inheritance reported

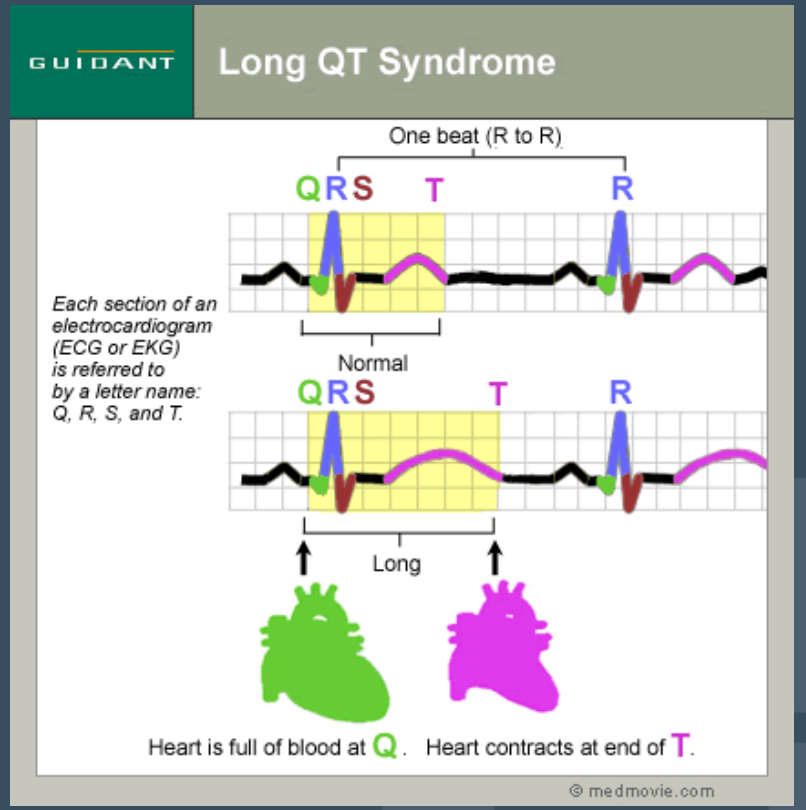
Prevalence: Pendred syndrome accounts for 6% of all congenital deafness

Inheritance: Autosomal recessive, however only one *SLC26A4* variant is found in up to 25% of cases…

Jervell and Lange-Neilson syndrome (JLNS)

- **Hearing Loss**
  - Congenital, bilateral, profound sensorineural HL
- **Long QT syndrome**
  - Prolonged QTc intervals on echocardiogram
  - Can lead to ventricular arrhythmias and sudden death

- These individuals should be under care of a cardiologist
- Treatment: beta blockers or implantable defibrillators
  - >50% of untreated individuals die <15 years



Jervell and Lange-Neilson syndrome

- Diagnosis should be considered in any child with congenital SNHL
  - EKG is typically ordered
- When taking pedigree:
  - Family history of syncope
  - Family history of seizures
  - Family history of sudden death
- Heterozygotes usually have normal hearing
  - Long QT Syndrome
- Genes:
  - *KCNQ1*(11p15) - >90% of individuals with JLNS
  - *KCNE1*(21q22) - ~10% of individuals with JLNS

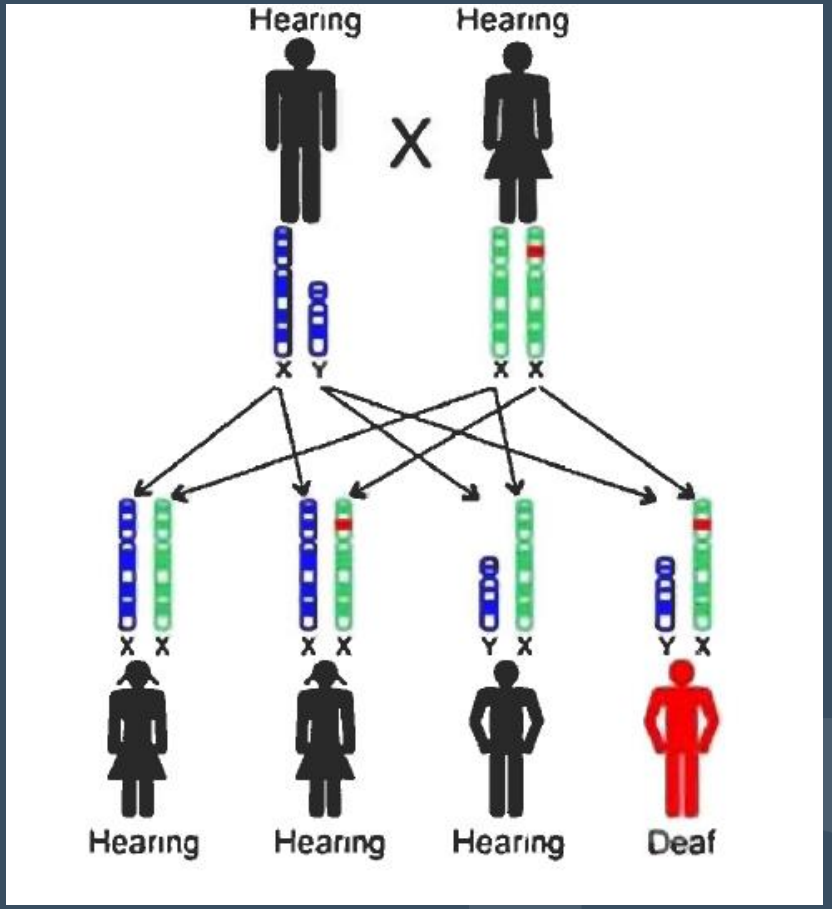
Other Syndromes

Maternally Inherited Diabetes and Deafness (MIDD)

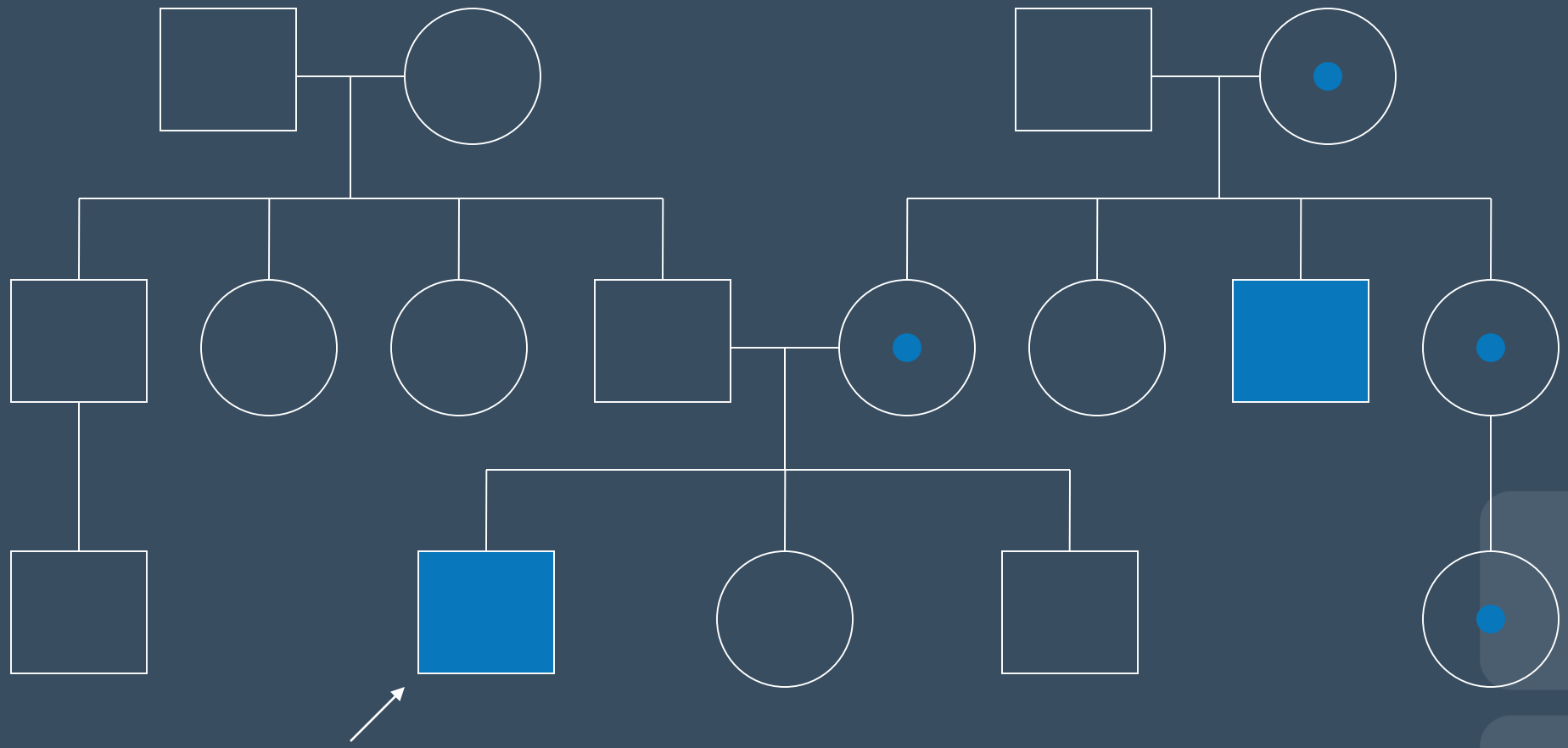
- High frequency hearing loss and diabetes
- Variable
- Mitochondrial condition *MT-TL1, MT-TK, MT-TE*

Alport Syndrome

- **Kidney disease**
  - Hematuria (blood in urine) often first symptom
  - Typically progresses to end stage renal disease
- **Sensorineural hearing loss**
  - HL typically presents late childhood, progressive
- **Ocular findings**
  - Anterior lenticonus (15-20%) - highly characteristic of the syndrome



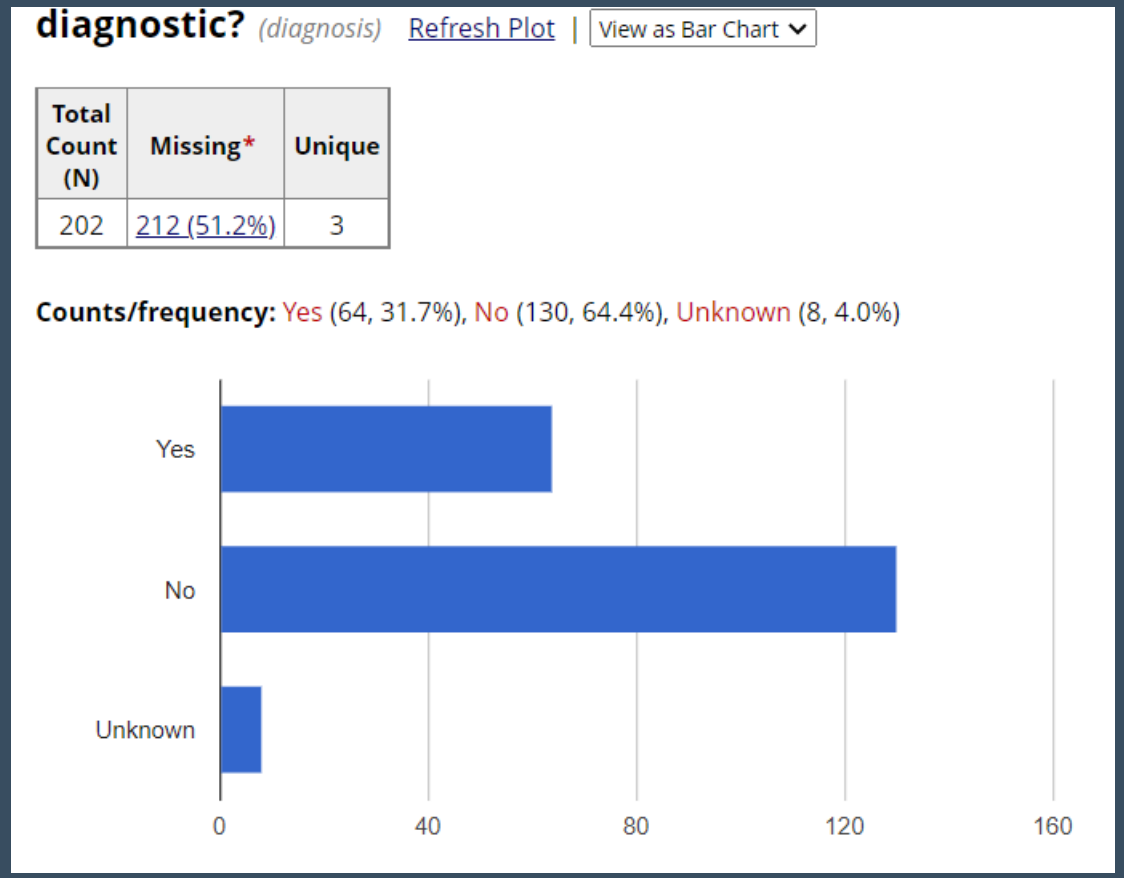
X-linked



Alport Syndrome

- 85% - X-linked (*COL4A5*)
  - 10-15% of individuals with XL form have a de novo variant
  - Males are more severe (female carriers can have hematuria and adult onset hearing loss)
- 15% - AR (*COL4A3, COL4A4*)
  - No difference between males and females in severity of kidney disease or hearing loss
- <5% - AD (*COL4A3, COL4A4*)
  - Seeing more frequently in renal genetics clinic…
  - Hearing loss not as prominent in AD Alport

Preliminary data:

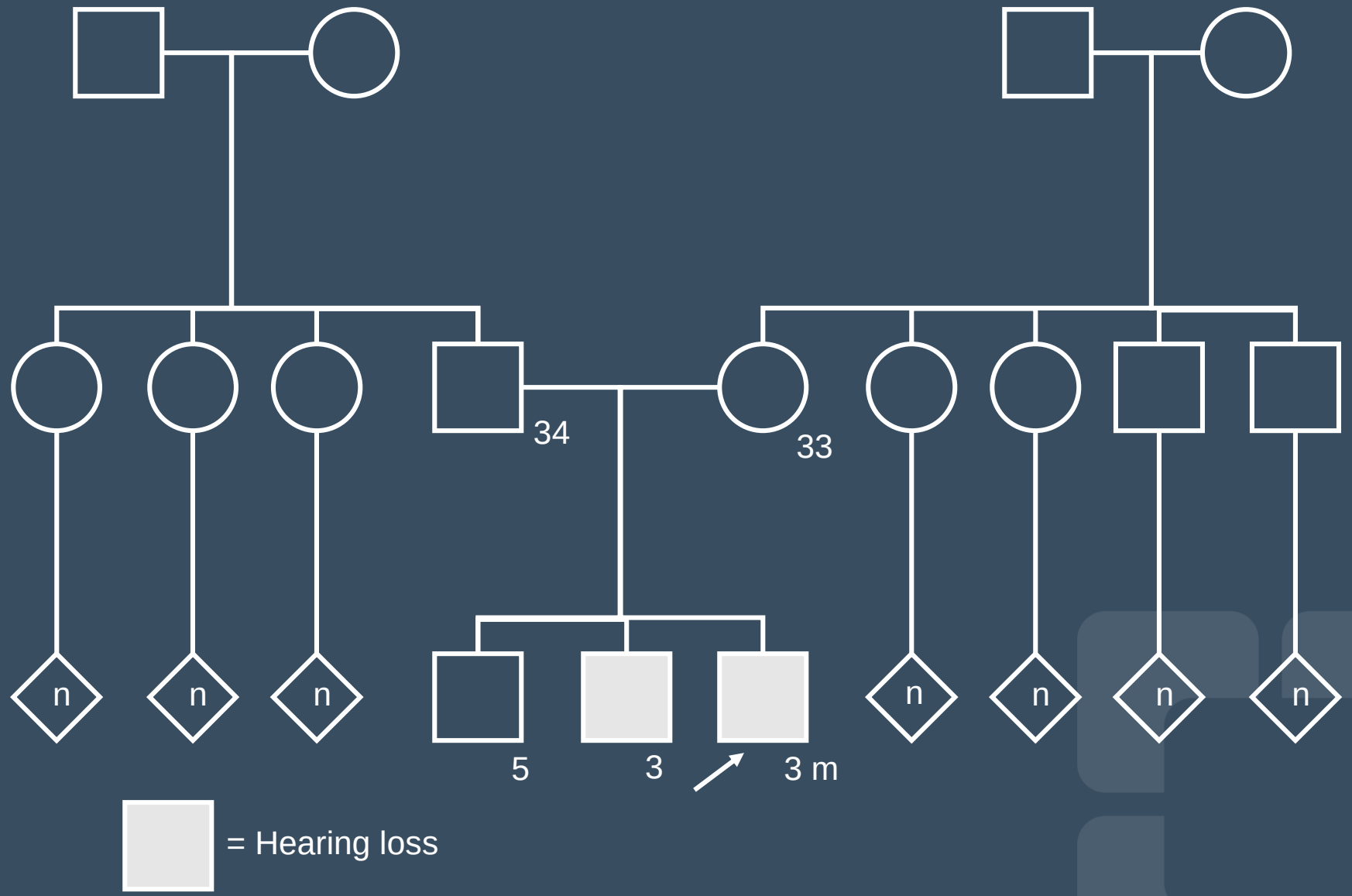


- 414 patients logged (from 2008 to August 2022)
- From the 212 patients that completed genetic testing 32% diagnostic rate
- 98 of 414 no genetic testing was recommended
- other 104 either declined, never had blood drawn, or insurance denial

Case Examples

Case 1

- 3-month-old boy who failed newborn hearing screen
- Diagnosed with bilateral severe to profound SNHL
- One brother with congenital hearing loss

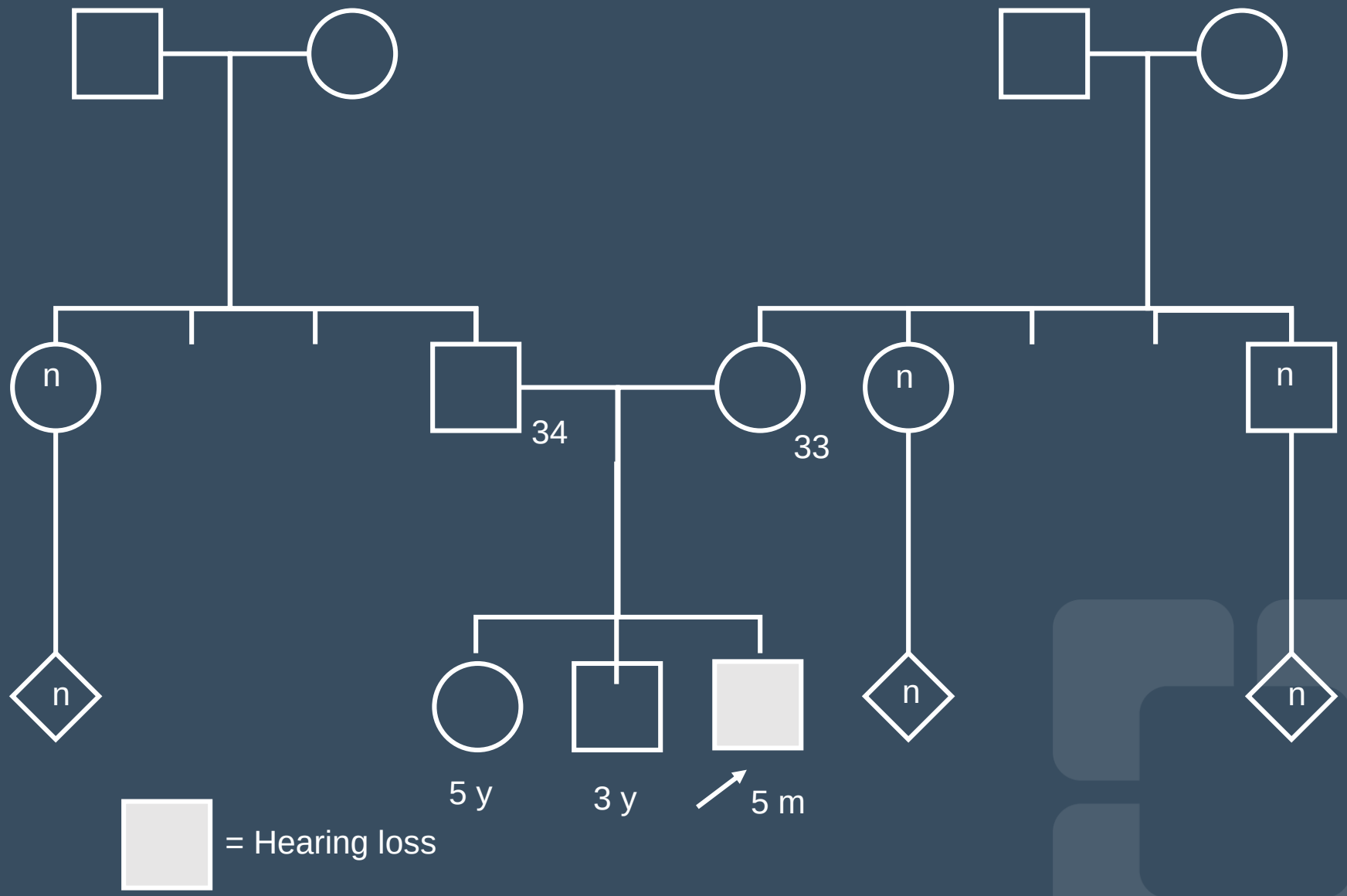


Connexin 26

- Homozygous pathogenic variants in *GJB2* gene
- Each child had a 25% chance
- Their children will only be affected if their partners have a *GJB2* variant

Case 2

- 5m old male failed NBHS
- Mild-mod b/l SNHL
- Workup otherwise normal

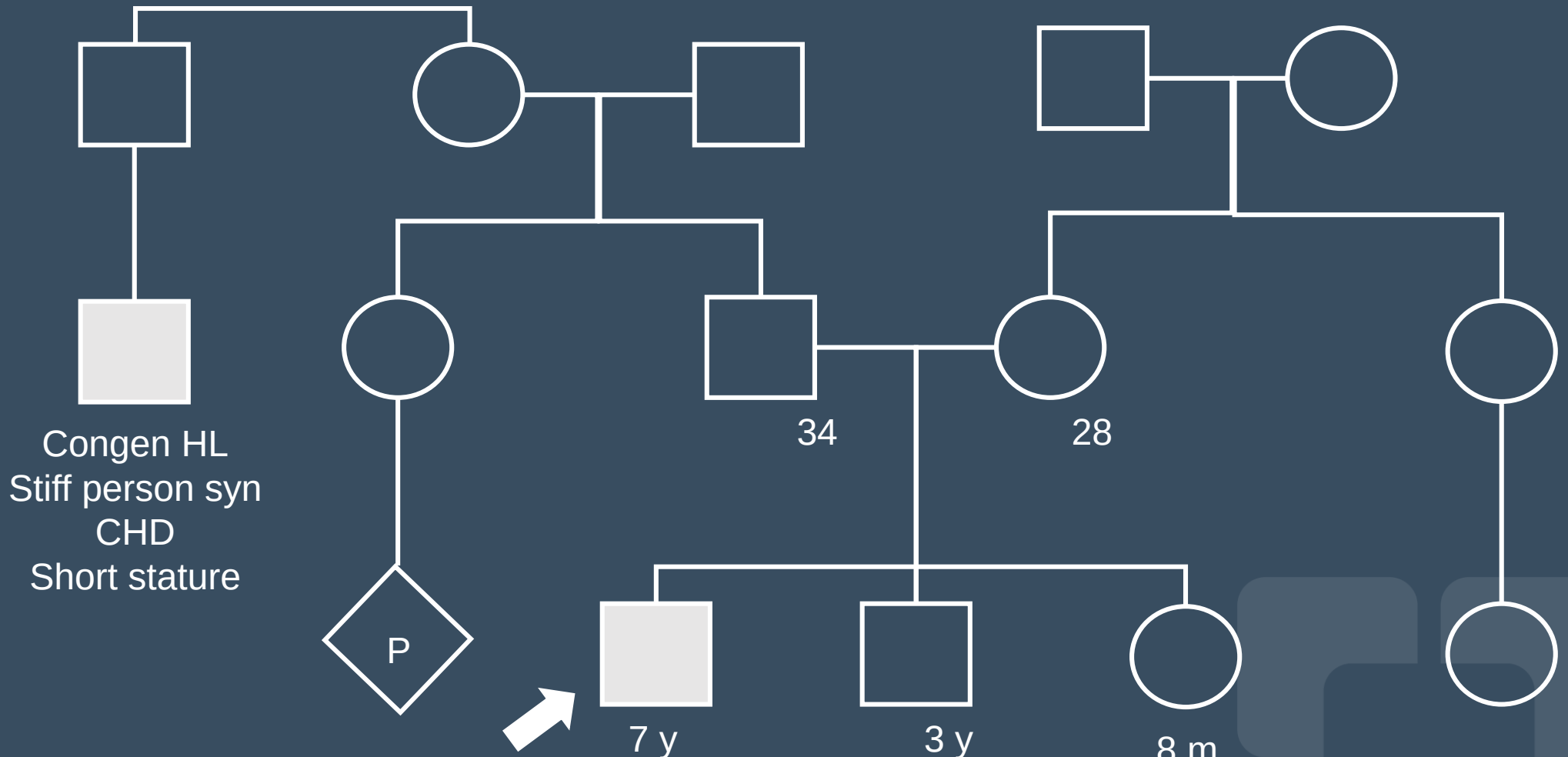


Case 2

- HL panel results - *USH2A* pathogenic variants consistent with a diagnosis of Usher syndrome type 2
- Currently 3y old and starting to show retina abnormalities with ophthalmology
- Brother and sister had negative testing (not carriers)

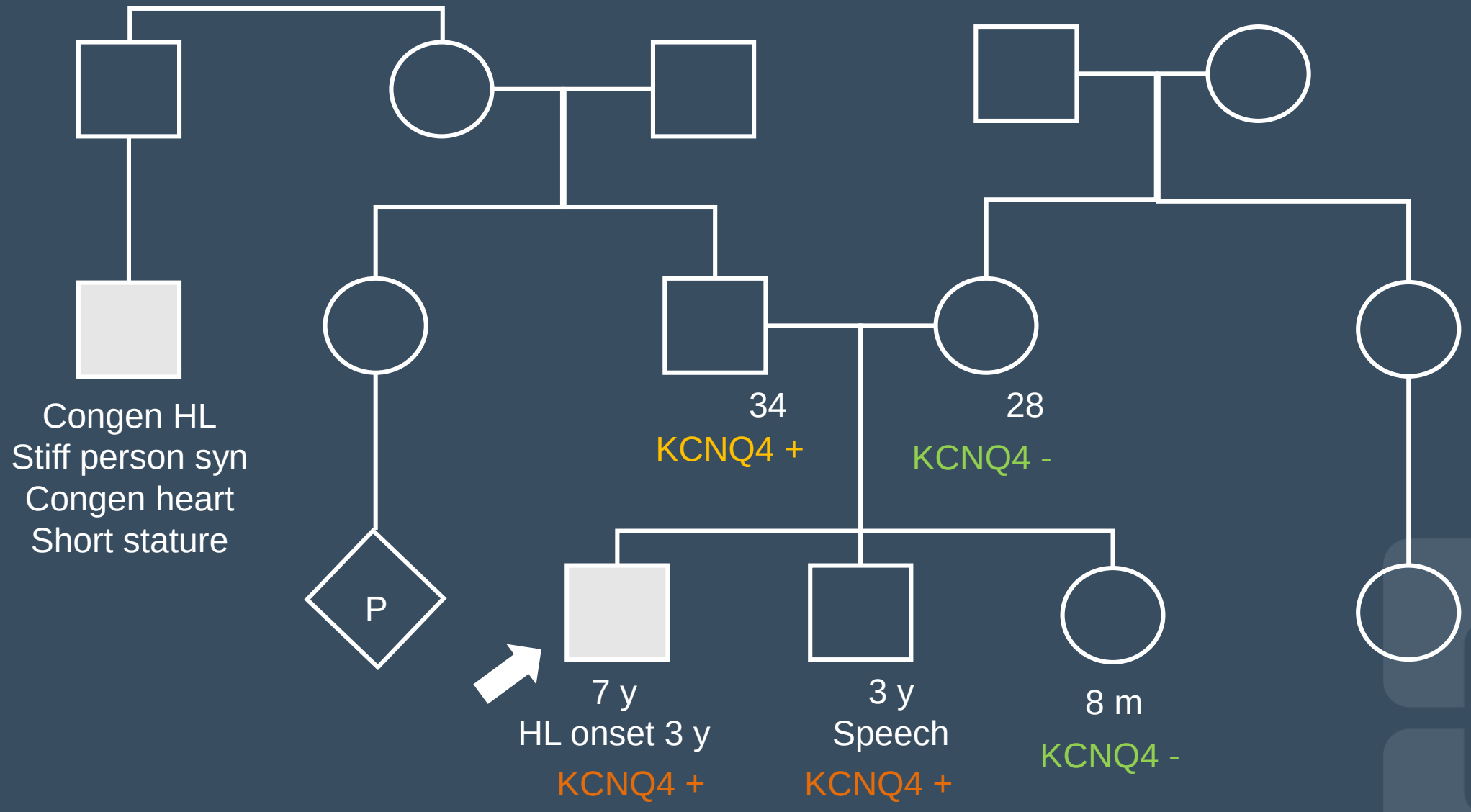
Case 3

7 year old male with moderate hearing loss, onset 3 years of age



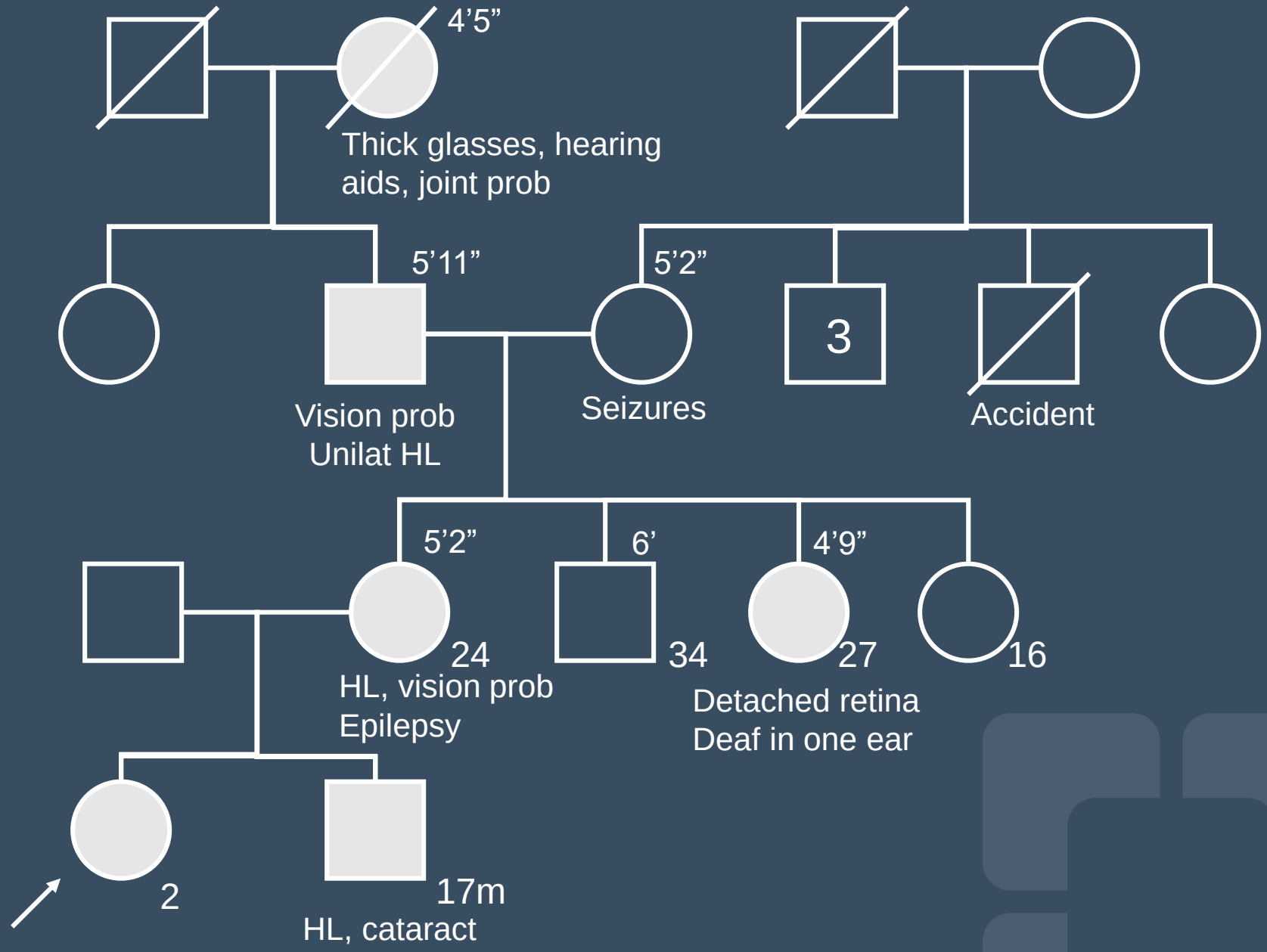
Case 3

- *KCNQ4* Likely pathogenic variant
- Non-syndromic autosomal dominant hearing loss
- Onset typically in childhood, higher frequencies
- Often progressive but variable


Congen HL
Stiff person syn
Congen heart
Short stature
P
34
KCNQ4 +
28
KCNQ4 -
7 y
HL onset 3 y
KCNQ4 +
3 y
Speech
KCNQ4 +
8 m
KCNQ4 -

Case 4

2-year-old girl with hearing loss, high myopia, short stature, dysmorphic features

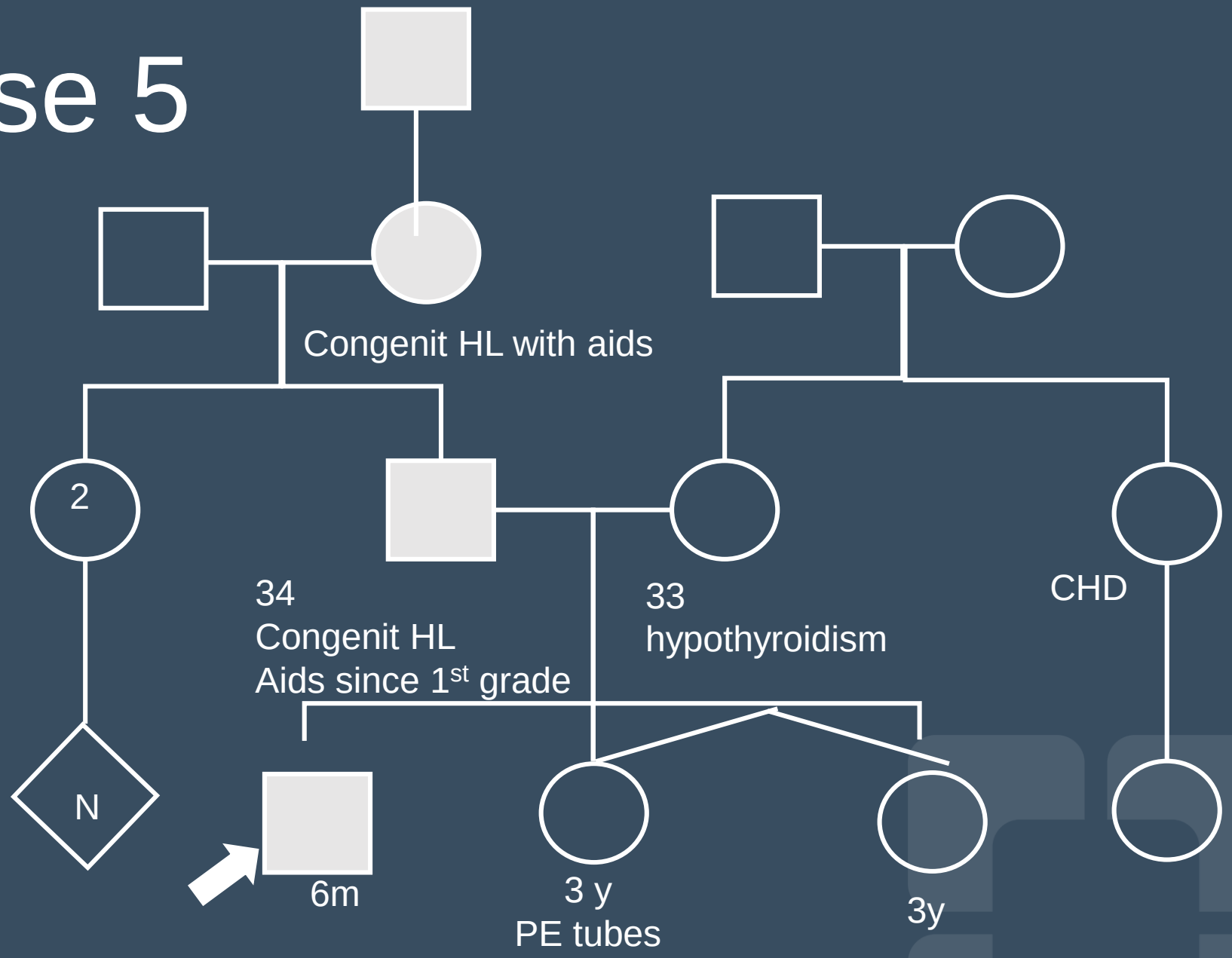


Stickler Syndrome

- Pathogenic variant in the *COL2A1* gene
- At risk for retinal detachment, arthritis
- Family cascade testing

Case 5

- 6m male congenital b/l SNHL
- Failed NBHS
- Wearing aids
- Hypospadias repaired at 6m
- Pediatrician and ENT noted b/l preauricular pits



Case 5

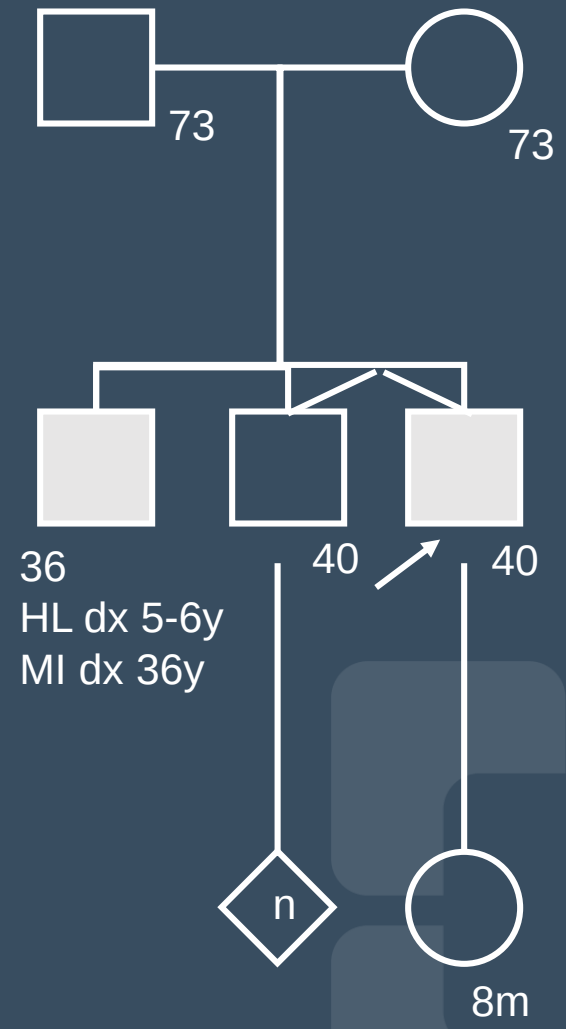
- HL panel – identified pathogenic variant in *SIX1* consistent with diagnosis of Branchio-oto-renal syndrome type 3 (OMIM #605192)
- Reviewed variability, majority nonprogressive (~70%), genotype-phenotype (*SIX1* related BOR typically no renal findings)
- Recommended kidney US, nephrology baseline
- Testing for sisters for BOR due to variability, and father
- Also found to be carrier for *GJB2* – discussed AR also

Case 6

- 40y male with profound b/l SNHL
- Progressive HL, first dx at 6y, recalls being able to hear on the phone as a child
- Had a single hearing aid he would alternate ears with
- 1m before visit had CI (after daughter was born)

No other known family members with HL

Limited family history knowledge, family moved to US when child



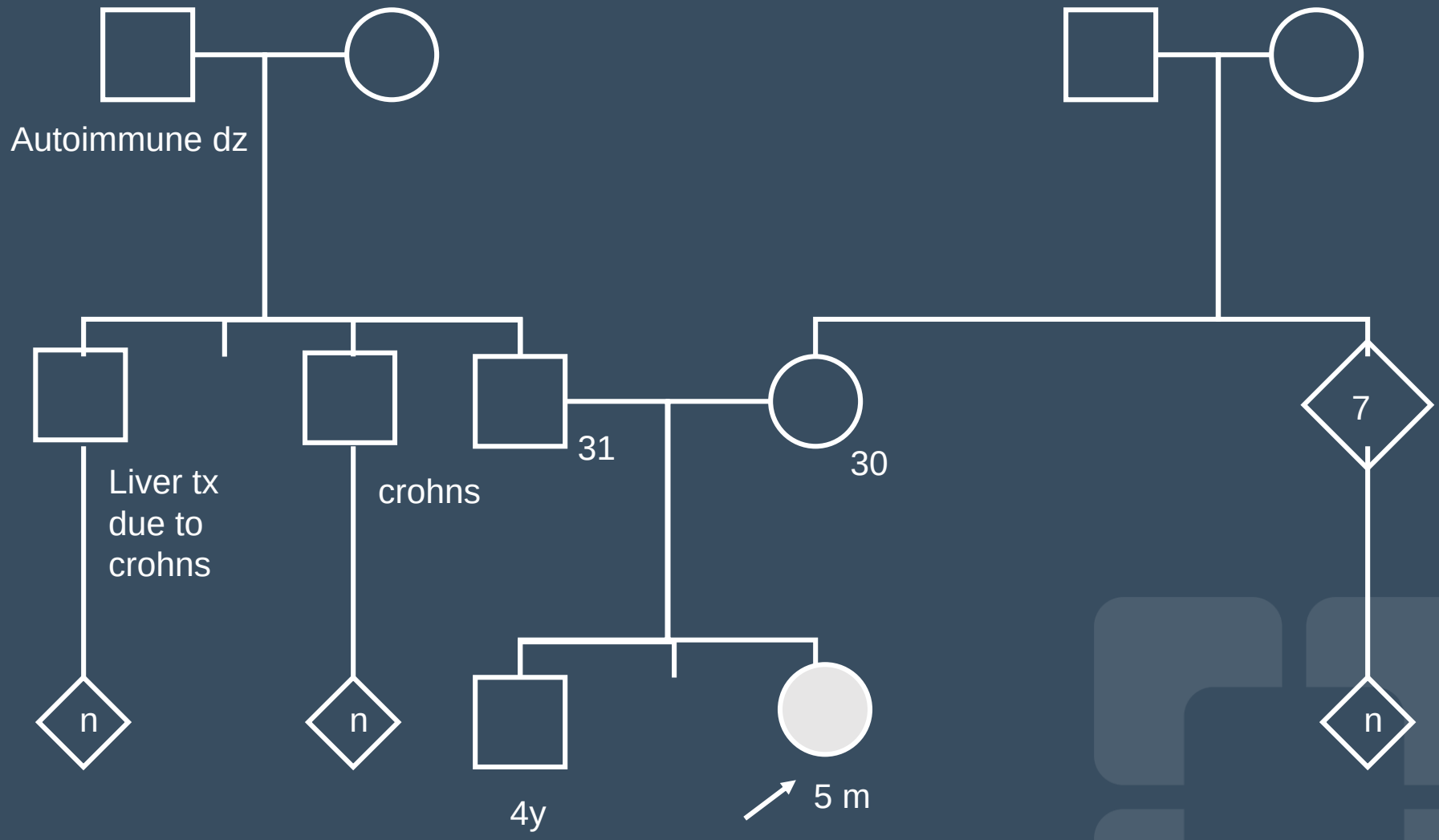
= Hearing loss

Case 6

- HL Panel – two pathogenic variants identified in *MYO15A*
- Associated with AR nonsyndromic HL
- Clinical presentation is typically prelingual, severe to profound, and stable
- Family letter for brothers, carrier testing for his wife

Case 7

- 5m female with b/l SNHL after failed NBHS
- Connexin negative, reflexed to panel
- While results pending, imaging noted dysplastic b/l vestibules, semicircular canals
  - Updated lab



Case 7

- HL panel – *GREB1L* pathogenic variant
- New association with HL – 2 papers reporting on 4 individuals with profound SNHL and innear ear malformations
  - (Schrauwen et al., 2020; Schrauwen et al., 2018)
- 3 papers report on *GREB1L* association for renal anomalies (agenesis, horseshoe kidney, etc)
  - (Jacquinet et al., 2020; Brophy et al., 2017; Sanna-Cherchi et al., 2017)
  - One case with severe kidney disease and u/l HL
  - Variant specific phenotype hypothesis
- Autosomal dominent – 2 de novo, 2 inherited (one unaffected parent) – possibility of reduced penetrance
  - Recommended parent testing

Case 7

- *GREB1L* is a new gene association
- Version 8 = 152 genes
- Version 9 = 224 genes
- If testing was ordered 2 months before, this patient wouldn’t have a diagnosis
- Highlights reason for patients to return to genetics periodically (~every few years)

Questions?

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