Clinical Impact of Genetics in Sensorineural hearing Loss

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EHDI Conference
March 15, 2022
2:30-3:00 pm MST

UCSF Benioff Children's Hospital San Francisco

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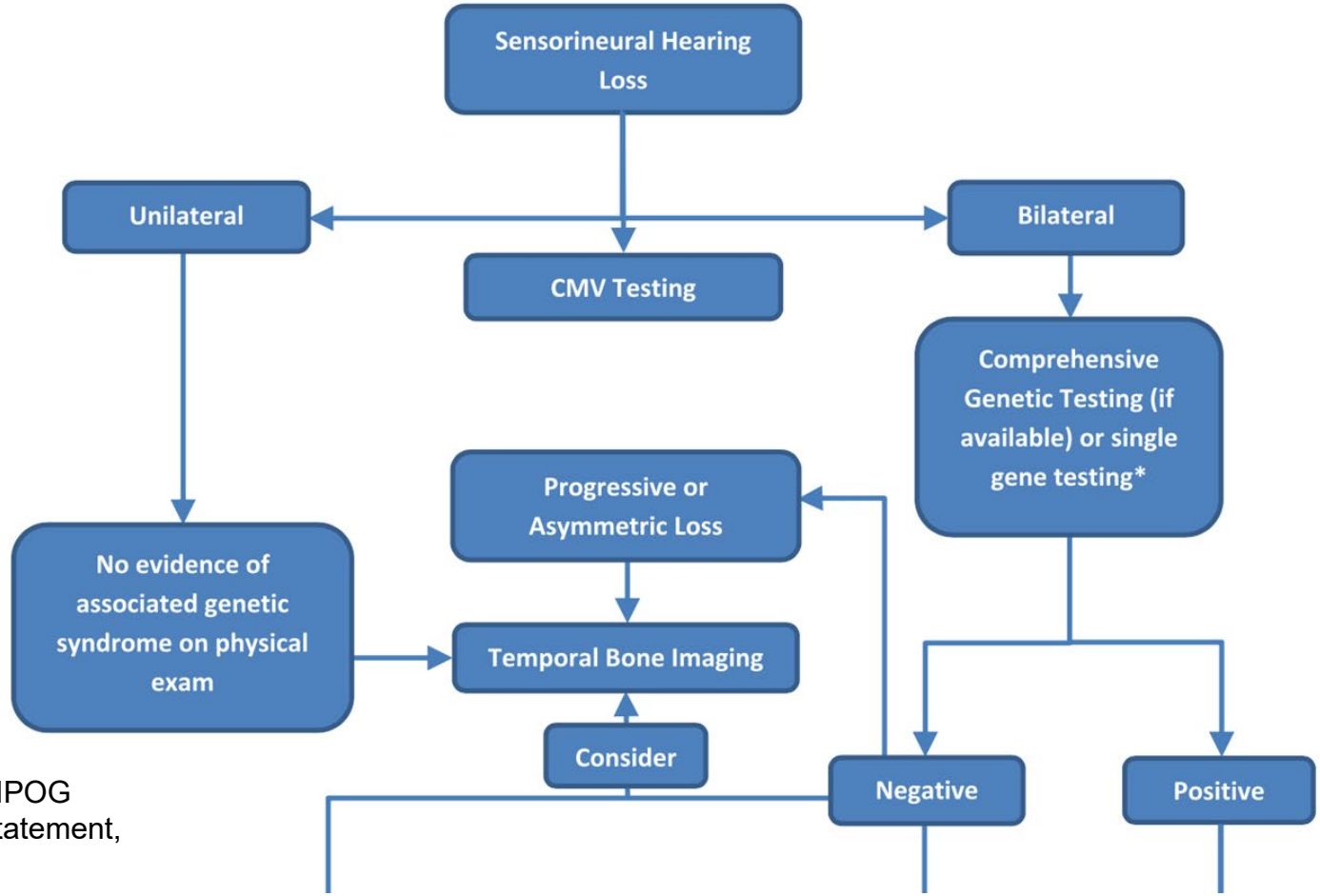
Conflict of Interest

- The presenters have no conflicts of interest

Outline

- Genetic testing in children who are D/HH
- The impact of genetic knowledge on management of D/HH
- Case studies
- Questions

Genetic Testing Who? When?



Liming et al., IPOG Consensus Statement, 2016

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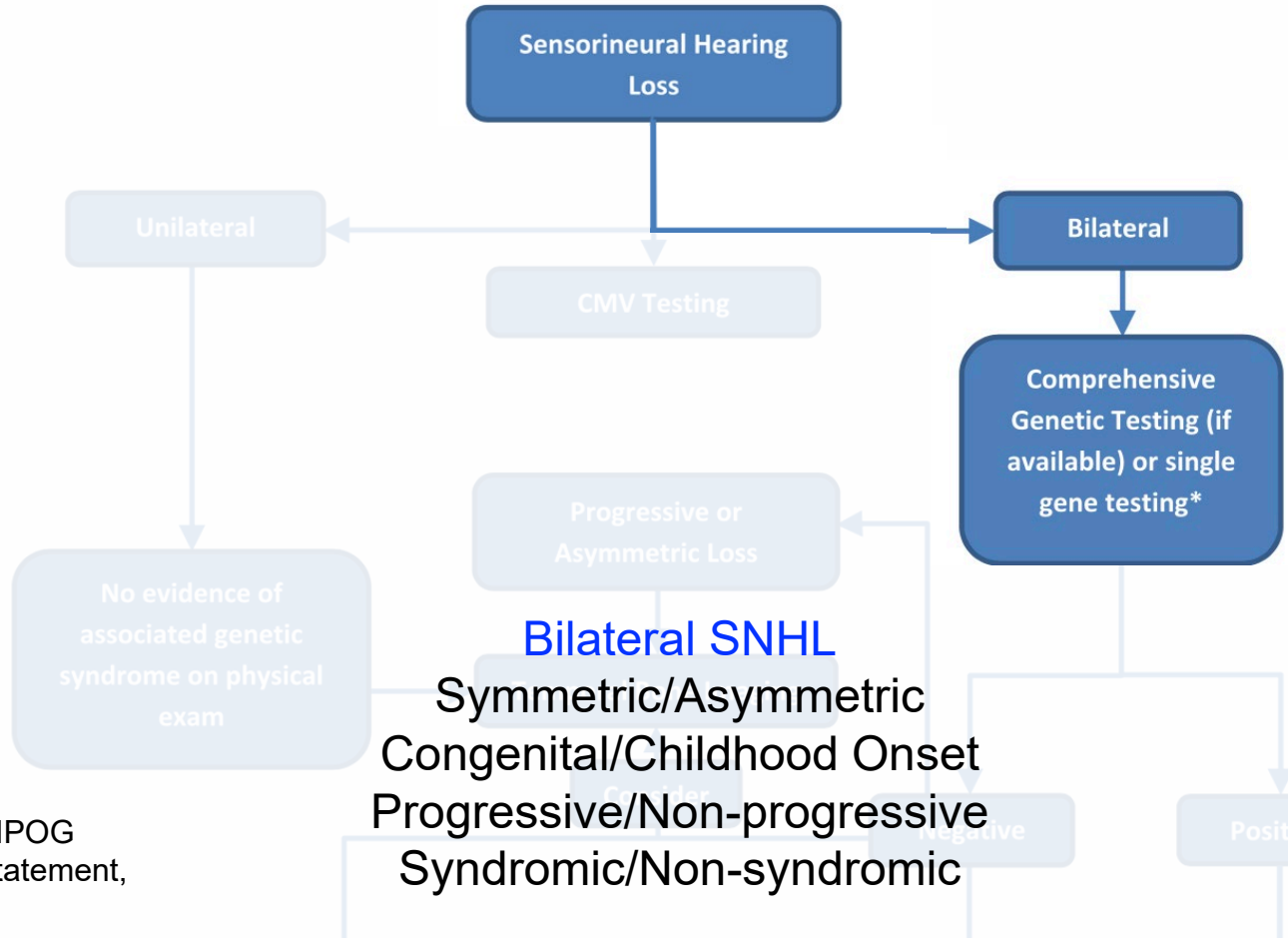
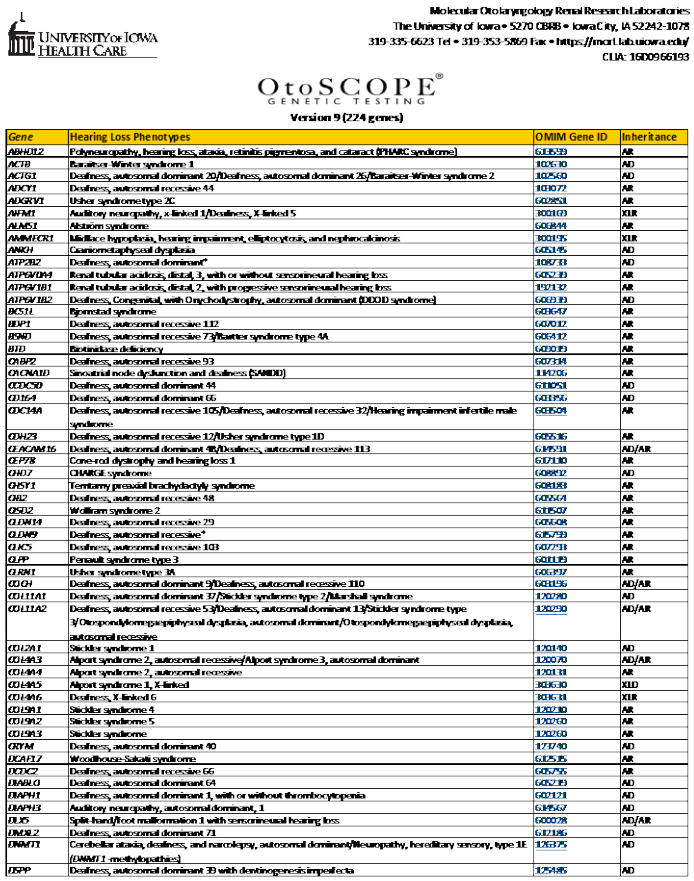


Bilateral SNHL
Symmetric/Asymmetric
Congenital/Childhood Onset
Progressive/Non-progressive
Syndromic/Non-syndromic

Liming et al., IPOG Consensus Statement, 2016

Genetic Testing How?



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OtoSCOPE® GENETIC TESTING

Version 9 (224 genes)

Gene	Hearing Loss Phenotypes	OMIM Gene ID	Inheritance
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC syndrome)	613599	AR
ACTB	Baraitser-Winter syndrome 1	102630	AD
ACTG1	Deafness, autosomal dominant 20/Deafness, autosomal dominant 26/Baraitser-Winter syndrome 2	102560	AD
ADCY1	Deafness, autosomal recessive 44	103072	AR
ADGRV1	Usher syndrome type 2C	602851	AR
AFF4	Auditory neuropathy, x-linked 1/Deafness, X-linked 5	300803	XLR
ALMS1	Alstrom syndrome	606844	AR
AMMECR1	Midface hypoplasia, hearing impairment, elliptocytosis, and nephrocalcinosis	300195	XLR
ANKH	Craniometaphyseal dysplasia	605145	AD
ATP2B2	Deafness, autosomal dominant*	108733	AD
ATP6V0B4	Renal tubular acidosis, distal, 3, with or without sensorineural hearing loss	606939	AR
ATP6V1B1	Renal tubular acidosis, distal, 2, with progressive sensorineural hearing loss	192132	AR
ATP6V1B2	Deafness, Congenital, with Onychodystrophy, autosomal dominant (DDOD syndrome)	600938	AD
BCS1L	Bjornstad syndrome	603647	AR
BDP1	Deafness, autosomal recessive 112	607097	AR
BSND	Deafness, autosomal recessive 73/Bartter syndrome type 4A	606412	AR
BTD	Biotinidase deficiency	609019	AR
CABP2	Deafness, autosomal recessive 93	607314	AR
CACNA1D	Sinoatrial node dysfunction and deafness (SANDD)	114206	AR
CDC50	Deafness, autosomal dominant 44	611651	AD
CD164	Deafness, autosomal dominant 66	603356	AD
CDC14A	Deafness, autosomal recessive 105/Deafness, autosomal recessive 32/Hearing impairment infertile male syndrome	603504	AR
CDH23	Deafness, autosomal recessive 12/Usher syndrome type 1D	605516	AR
CLCAM16	Deafness, autosomal dominant 48/Deafness, autosomal recessive 113	614931	AD/AR
CEP78	Cone-rod dystrophy and hearing loss 1	617130	AR
CHD7	CHARGE syndrome	608892	AD
CHSY1	Temtamy preaxial brachydactyly syndrome	608183	AR
CIB2	Deafness, autosomal recessive 48	609439	AR
COL2	Williram syndrome 2	616507	AR
CLDN14	Deafness, autosomal recessive 29	604418	AR
CLDN9	Deafness, autosomal recessive*	605723	AR
CLIC5	Deafness, autosomal recessive 103	607931	AR
CLPP	Perrault syndrome type 3	601119	AR
CLRN1	Usher syndrome type 3A	606397	AR
COCH	Deafness, autosomal dominant 9/Deafness, autosomal recessive 110	603196	AD/AR
COL11A1	Deafness, autosomal dominant 37/Stickler syndrome type 2/Marshall syndrome	120280	AD
COL11A2	Deafness, autosomal recessive 53/Deafness, autosomal dominant 13/Stickler syndrome type 3/Otospondylomespiphyseal dysplasia, autosomal dominant/Otospondylomespiphyseal dysplasia, autosomal recessive	120290	AD/AR
COL2A1	Stickler syndrome 1	120140	AD
COL4A3	Alport syndrome 2, autosomal recessive/Alport syndrome 3, autosomal dominant	120070	AD/AR
COL4A4	Alport syndrome 7, autosomal recessive	120131	AR
COL4A5	Alport syndrome 1, X-linked	303630	XLD
COL4A6	Deafness, X-linked 6	300514	XLR
COL9A1	Stickler syndrome 4	120210	AR
COL9A2	Stickler syndrome 5	120260	AR
COL9A3	Stickler syndrome	120270	AR
CRYM	Deafness, autosomal dominant 40	123740	AD
DCAF17	Woodhouse-Sakati syndrome	612515	AR
DCDC2	Deafness, autosomal recessive 66	605755	AR
DIABLO	Deafness, autosomal dominant 64	605219	AD
DIAPH1	Deafness, autosomal dominant 1, with or without thrombocytopenia	602121	AD
DIAPH3	Auditory neuropathy, autosomal dominant, 1	614626	AD
DLX5	Split-hand/foot malformation 1 with sensorineural hearing loss	600028	AD/AR
DMXL2	Deafness, autosomal dominant 71	612186	AD
DNMT1	Cerebellar ataxia, deafness, and narcolepsy, autosomal dominant/Neuropathy, hereditary sensory, type 1E (*DNMT1*-methylopathies)	126375	AD
DSPP	Deafness, autosomal dominant 39 with dentinogenesis imperfecta	125485	AD

Single Gene/Targeted Panels

- GJB2
- Pendred, Ushers

Comprehensive hearing-loss panels

120-220 genes

- Targeted capture/massively parallel sequencing
- Deletion/duplication analysis
- Copy number analysis

Otoscope (U of Iowa)
GeneDx
Invitae
Multiple others

Cheek swab or blood test

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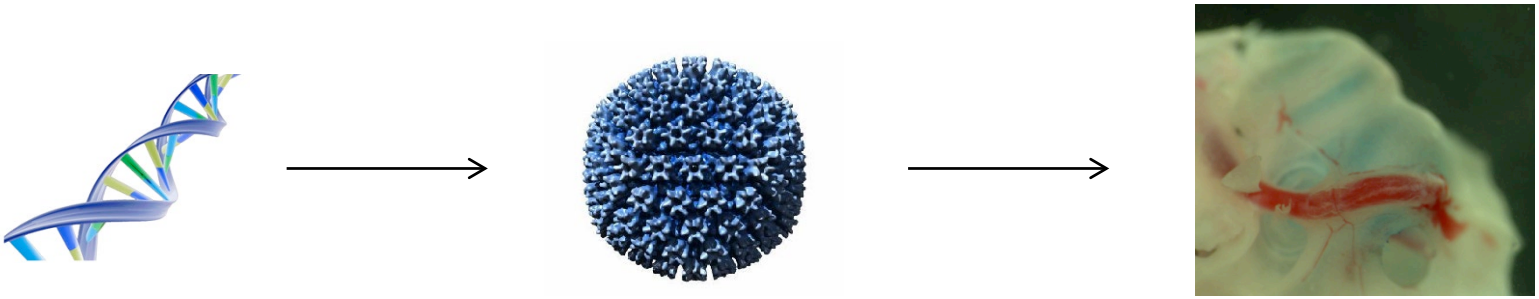
Genetic Testing Why?

Any cause identified	Genetic counseling, education, acceptance
Specific genes/variants	Hearing expectations: progression, ototoxicity, cochlear implant outcomes
Future management options	Cochlear implantation, gene therapy
Syndromic association identified	Early screening for associated differences



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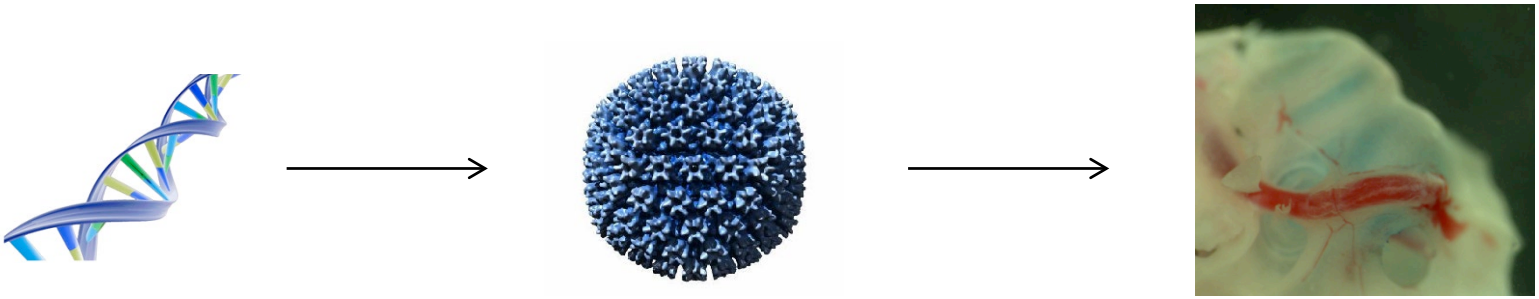

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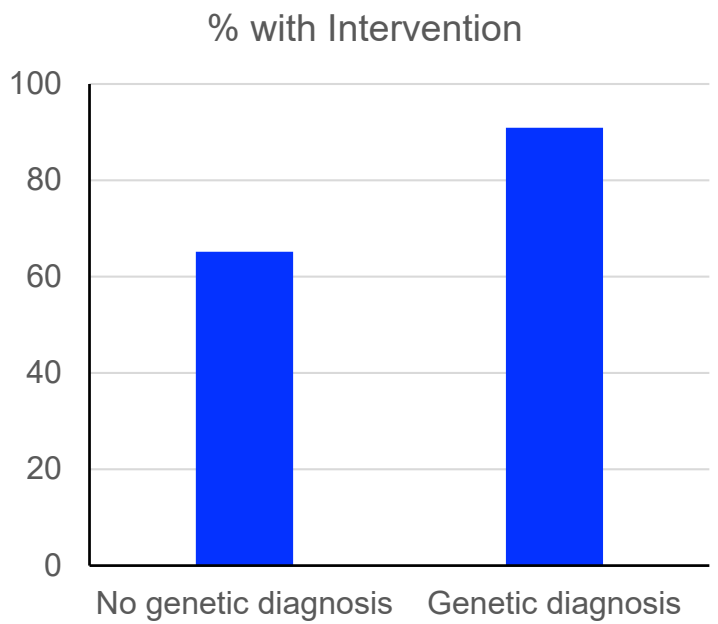

Brodie and Chan, unpublished

111 children with SNHL

Genetic testing before hearing aid evaluation

73% Underrepresented minorities
67% Publicly insured

20% Genetic diagnosis

Receiving a genetic diagnosis associated with increased likelihood to be fit with HA

Adjusted for hearing level, insurance, race/ethnicity

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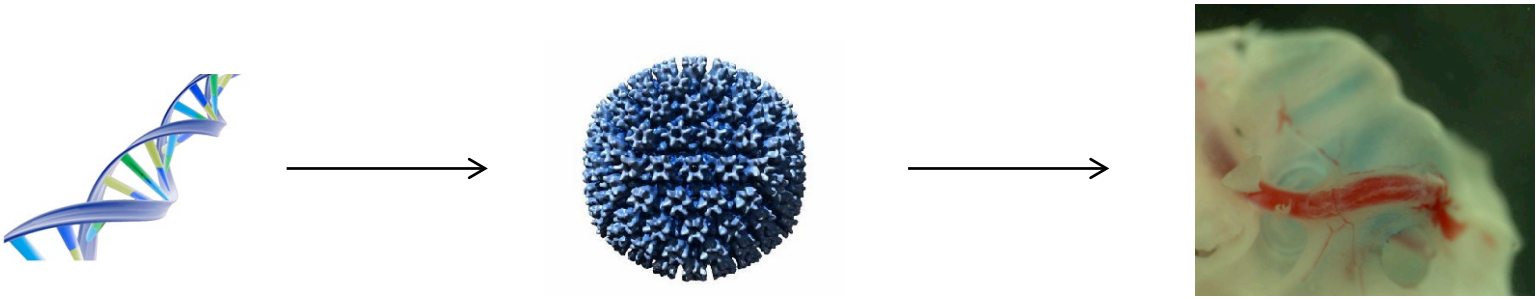
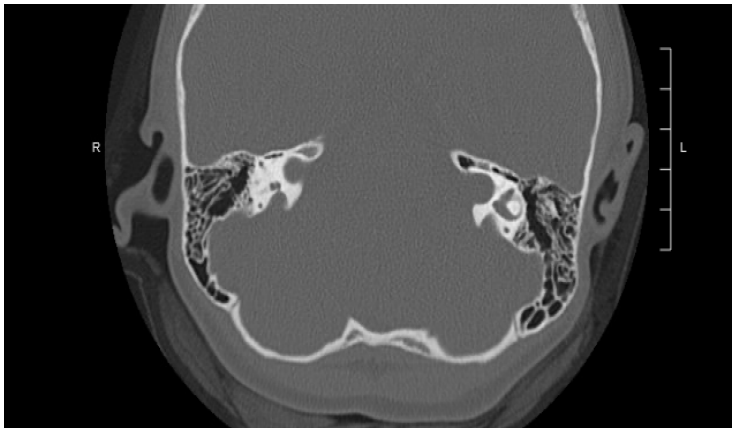


Genetic Testing Progressive Hearing Loss



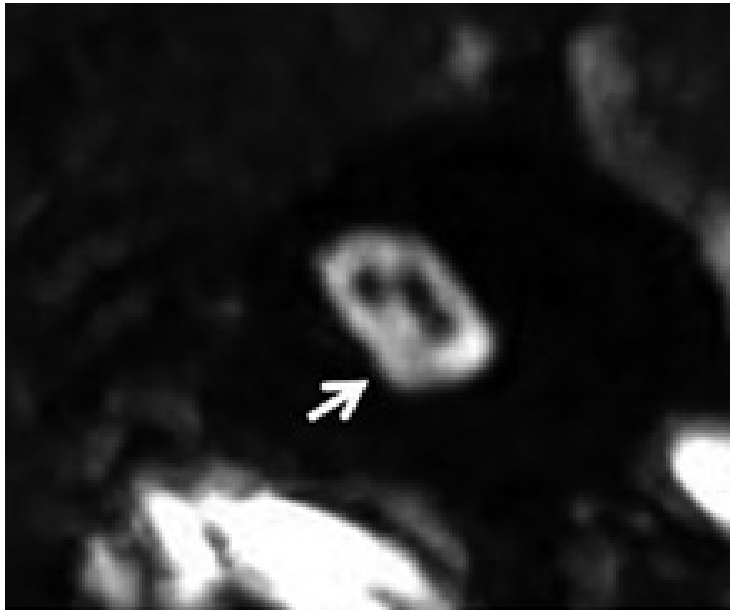
Progressive

SLC26A4
TECTA
Taperin
Mir95

(Mostly) Non-progressive

GJB2
STRC
OTOG

Genetic Testing Management Outcomes



Auditory Neuropathy Spectrum Disorder (ANSD)

Highly variable presentation and outcomes

Common etiologies:

1) Cochlear nerve deficiency

Poor cochlear implant outcomes
Recommend ASL

2) Otoferlin variants (hair cell/neuron synapses)

Excellent cochlear implant outcomes
Impending gene therapy

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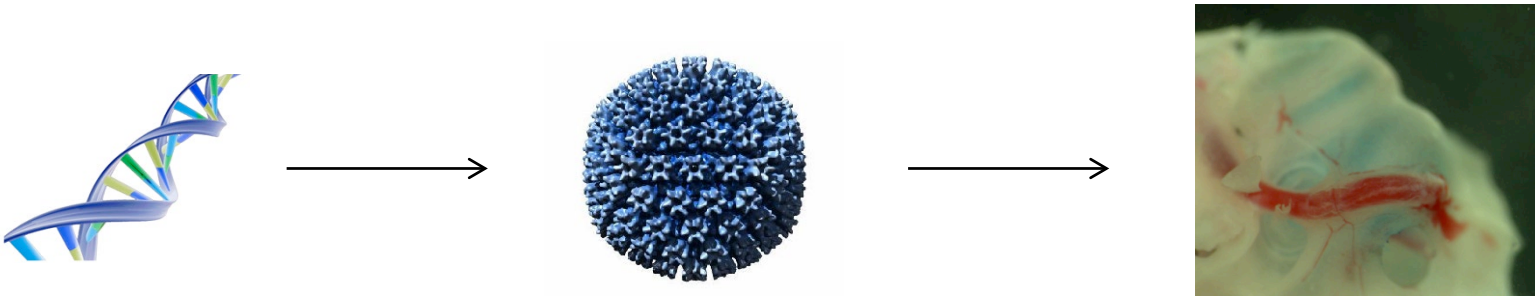
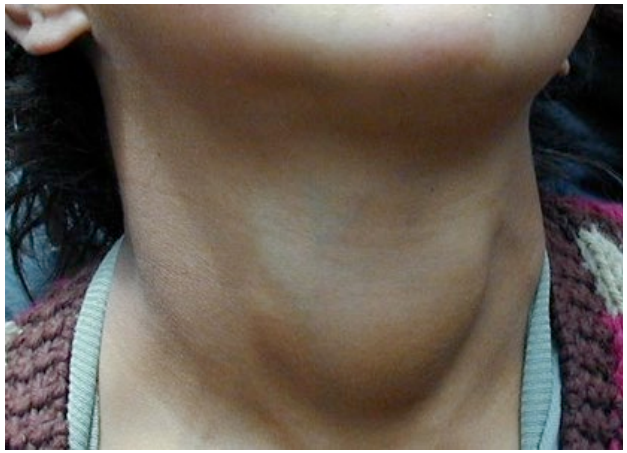


Genetic Testing Syndromic Discovery

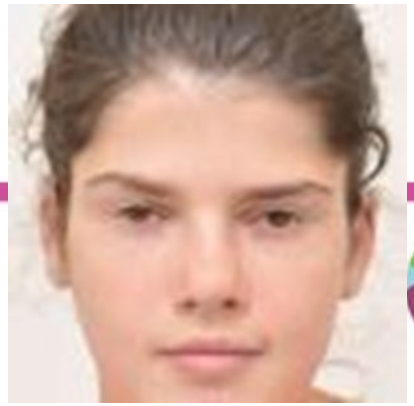


SLC26A4	Pendred
CDH23, Myo7a, USH2A…	Usher
COL11A1, COL11A2…	Stickler
COL4A3, COL4A4…	Alport
STRC/CATSPER	Deafness/infertility
EDN3, MITF, PAX3…	Waardenburg
EYA1, SIX5	Branchio-oto-renal
GATA3	Barakat

~3-5% of hearing-loss gene panels reveal a previously-unrecognized syndromic association

Genetic testing in children who are D/HH: looking beyond the ear

- Genetic testing alone does not replace the importance of an evaluation by a clinical geneticist
- Importance of dysmorphology: recognition of syndromes associated with hearing differences
- Among children who are Deaf/HH with an intellectual disability or autism spectrum disorder, we should not stop our genetic work-up at the level of the ear



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Genetic testing in children who are D/HH: looking beyond the ear

- Broader genetic evaluation, following the standard of care for work-up of developmental disabilities is important to remember
  - 3 generation family history, dysmorphology,
  - microarray, Fragile X, PTEN (macrocephaly), MECP2 (in girls), expanded genetic panels
  - Recognition of multiple congenital anomalies
  - Technology and knowledge is ever changing!

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

David T. Miller,[1,*] Margaret P. Adam,[2,3] Swaroop Aradhya,[4] Leslie G. Biesecker,[5] Arthur R. Brothman,[6] Nigel P. Carter,[7] Deanna M. Church,[8] John A. Crolla,[9] Evan E. Eichler,[10] Charles J. Epstein,[11] W. Andrew Faucett,[2] Lars Feuk,[12] Jan M. Friedman,[13] Ada Hamosh,[14] Laird Jackson,[15] Erin B. Kaminsky,[2] Klaas Kok,[16] Ian D. Krantz,[17] Robert M. Kuhn,[18] Charles Lee,[19] James M. Ostell,[8] Carla Rosenberg,[20] Stephen W. Scherer,[21] Nancy B. Spinner,[17] Dimitri J. Stavropoulos,[22] James H. Tepperberg,[23] Erik C. Thorland,[24] Joris R. Vermeesch,[25] Darrel J. Waggoner,[26] Michael S. Watson,[27] Christa Lese Martin,[2] and David H. Ledbetter[2,*]

The American Journal of Human Genetics 2010 86, 749–764

Original Investigation

Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder

Kristiina Tammimies, PhD; Christian R. Marshall, PhD; Susan Walker, PhD; Gaganjot Kaur, MRes; Bhooma Thiruvahindrapuram, MSc; Anath C. Lionel, PhD; Ryan K. C. Yuen, PhD; Mohammed Uddin, PhD; Wendy Roberts, MD; Rosanna Weksberg, MD-PhD; Marc Woodbury-Smith, MD-PhD; Lonnie Zwaigenbaum, MD; Evdokia Anagnostou, MD; Zhuozhi Wang, PhD; John Wei, PhD; Jennifer L. Howe; Matthew J. Gazzellone, MSc; Lynette Lau, MSc; Wilson W. L. Sung, MSc; Kathy Whitten; Cathy Vardy, MD; Victoria Crosbie, MD; Brian Tsang, BSc; Lia D'Abate, BSc; Winnie W. L. Tong; Sandra Luscombe, MD; Tyna Doyle, MD; Melissa T. Carter, MD; Peter Szatmari, MD; Susan Stuckless, PhD; Daniele Merico, PhD; Dimitri J. Stavropoulos, PhD; Stephen W. Scherer, PhD; Bridget A. Fernandez, MD

JAMA 2015 314(9):895-903

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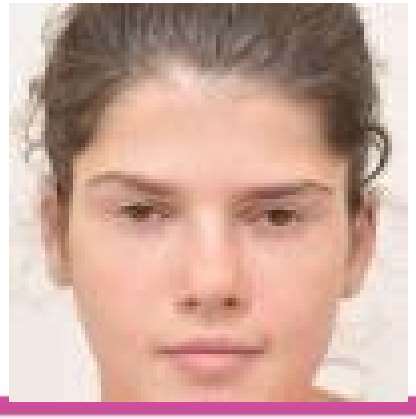
Impact of Genetic Knowledge on the management of children who are D/HH: broad-based genetic testing

- Goals of understanding genetic etiology:
- Recurrence risk for the individual, parents, siblings
- Associated medical conditions that may have been unrecognized



Case Studies

- a. Non-syndromic SNHL (GJB2) - Dylan
- b. Syndromic SNHL (Usher syndrome) - Dylan
- c. Developmental delay + SNHL - Susan

Case 1: CC

	LEFT EAR (dBeHL)	RIGHT EAR (dBeHL)
500 Hz tone burst ABR	15	15
1000 Hz tone burst ABR	15	30
2000 Hz tone burst ABR	15	35
4000 Hz tone burst ABR	15	25

2 mo old M
Full term
CMV negative
Club foot
No FH of hearing loss

Family uncertain of ABR findings
Declined Early Start and amplification

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Result(s): POSITIVE

GENE	MODE OF INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
GJB2	Autosomal dominant, Autosomal recessive	c.109 G>A p.(V37I)	Homozygous	Pathogenic Variant

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2 mo old M
Full term
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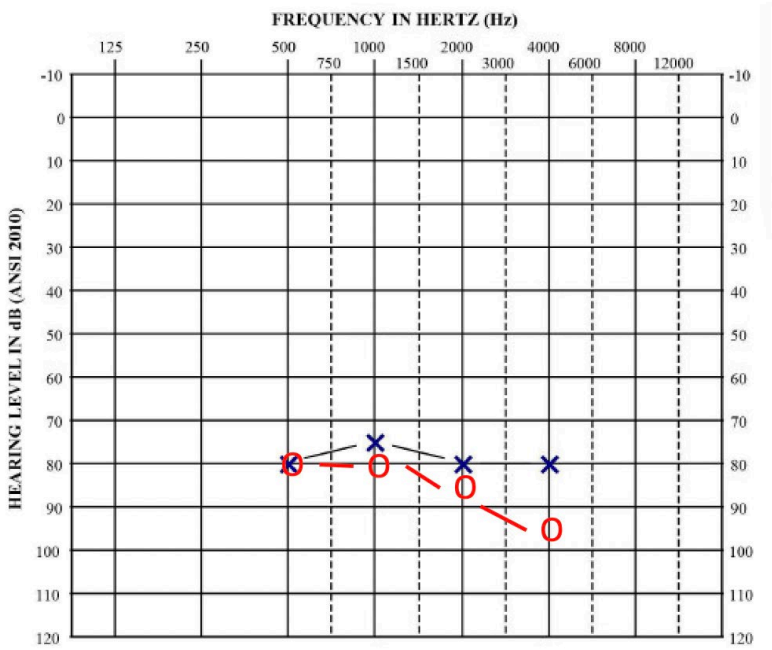
Declined Early Start and amplification

Genetics corroborates ABR
Rules out syndromic association

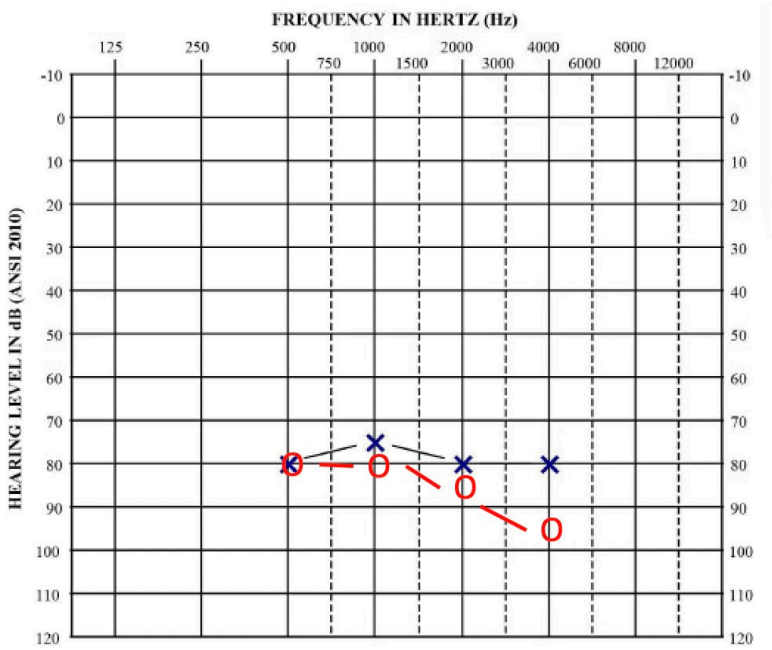
Enrolled in Early Start
Fit with R hearing aid

Case 2: LP



3 wk old F
Full term
CMV negative
MRI normal
Otherwise healthy
No FH of hearing loss

LP: Genetic Testing

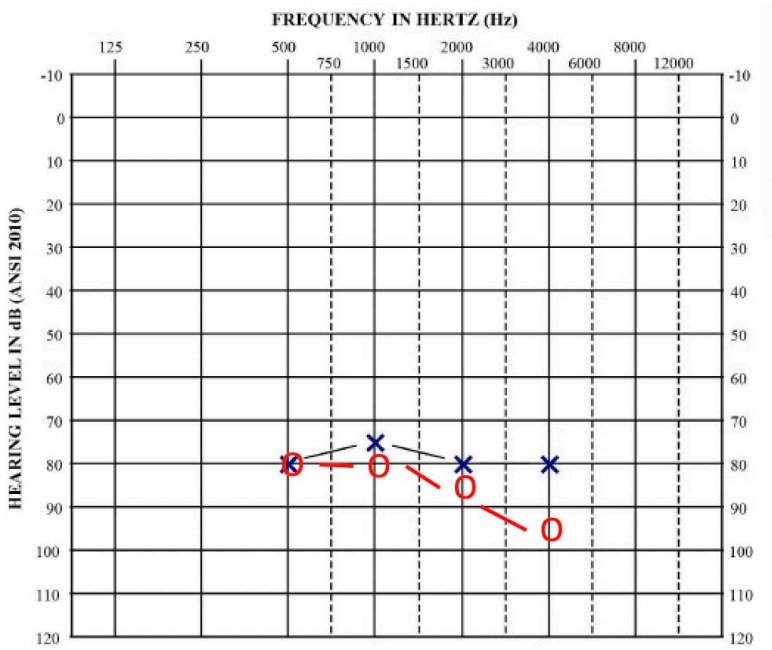


3 wk old F
Full term
CMV negative
MRI normal
Otherwise healthy
No FH of hearing loss

POSITIVE

Gene	Coding DNA	Variant	Zygosity	Classification
MYO7A	c.494 C>T	p.Thr165Met (T165M)	Heterozygous	Pathogenic Variant
MYO7A	c.321_322insA	p.Tyr108IlefsX32 (Y108IfsX32)	Heterozygous	Pathogenic Variant

LP: Genetic Testing Myo7A

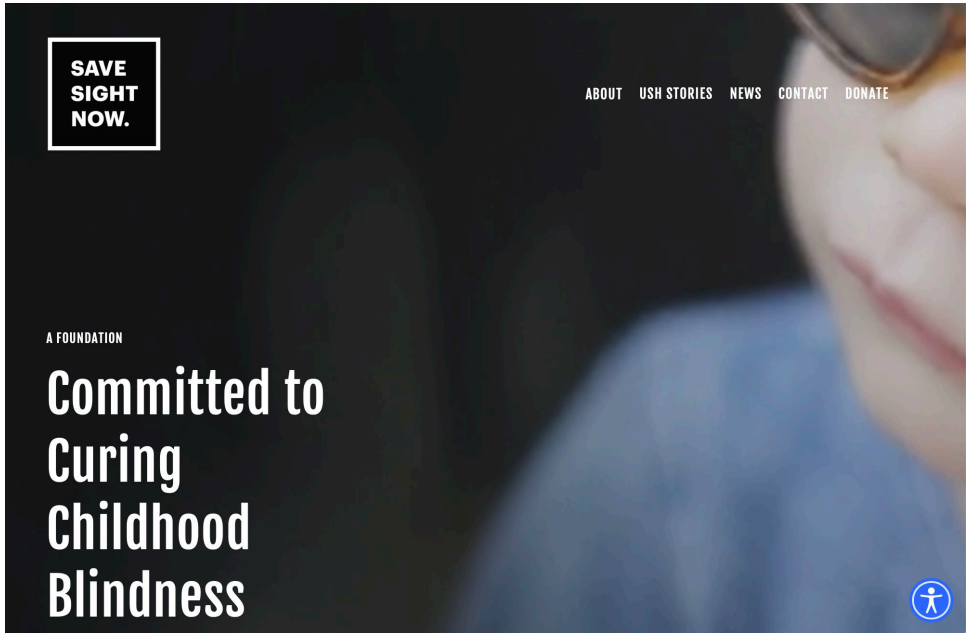


- NS-SNHL (DFNB2)
- Usher1B
- c.494 C>T: Usher1B
- c.321_322insA: unknown
- Parental testing confirms *trans*
- Ophthalmology referral
  - Normal ophtho exam
  - EUA: retinal dystrophy, maculopathy

POSITIVE

Gene	Coding DNA	Variant	Zygosity	Classification
MYO7A	c.494 C>T	p.Thr165Met (T165M)	Heterozygous	Pathogenic Variant
MYO7A	c.321_322insA	p.Tyr108IlefsX32 (Y108IfsX32)	Heterozygous	Pathogenic Variant

LP: Genetic Testing Myo7A



- Bilateral cochlear implantation
  - 6 months
  - Age-appropriate speech & language
- Ophthalmologic monitoring
  - Gene therapy (Sanofi NCT01505062)

Genetic Testing Leading to Early Identification of Childhood Ocular Manifestations of Usher Syndrome

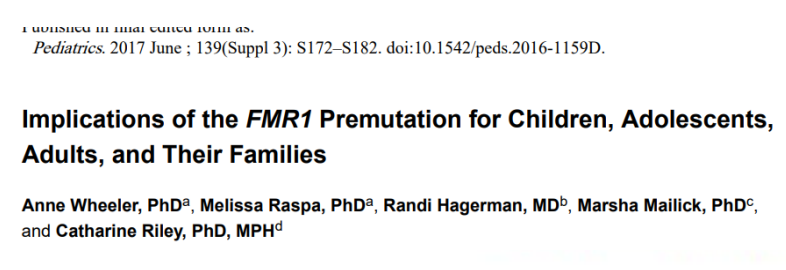
Kara D. Brodie, MD, MPhil; Anthony T. Moore, BM, BCh, FMedSci; Anne M. Slavotinek, MBBS, PhD; Anna K. Meyer, MD; Garani S. Nadaraja, MD; David E. Conrad, MD; Jacqueline E. Weinstein, MD; Dylan K. Chan, MD, PhD

Case study 3:

- First CI at 18 months and 2nd at 3 years
- Age of diagnosis of ID: 4 years of age:
  - Leiter score of 60, Vineland score of 58
- Age of diagnosis of ASD: 7 years of age
  - Evaluation at 4 years, thought to be related to ID rather than ASD, at 7 years, diagnosed with ASD
- Age of Usher Syndrome genetic finding: 10 years of age
  - An ERG at 10 years of age: evidence of early rod-cone degeneration but no functional impairment
  - At 18 years, has not had notable functional vision loss
- At of first seizure: 18 years of age

Case study 3:

- 5 years of age:
  - **Microarray results**: extra chromosomal material on 10q11.21
  - This region contains no known genes associated with pathology. Thought to most likely a benign copy number variant.
- 10 years of age:
  - **Fragile X testing**: Pre-mutation for Fragile X (CGG repeat size 56)
  - **Hearing gene pane**l: genetically confirmed MYO7A gene, compound heterozygote(both parents confirmed to be carriers
- 13 years of age
  - **Autism/ID expanded panel** negative



Children don't always follow what's in the books

COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

Hiding in plain sight: genetic deaf-blindness is not always Usher syndrome

Genevieve Medina,[1] Julia Perry,[1] Andrea Oza,[2,3] and Margaret Kenna[1,4]

Dammeyer *Behavioral and Brain Functions* 2012, **8**:16
http://www.behavioralandbrainfunctions.com/content/8/1/16

BBF BEHAVIORAL AND BRAIN FUNCTIONS

RESEARCH Open Access

Children with Usher syndrome: mental and behavioral disorders

Jesper Dammeyer[1,2]

Abstract

Background: Mental and behavioral disorders among adults with Usher syndrome have been discussed and reported in some case studies but no research has been reported on children with Usher syndrome.

Methods: This article investigates the prevalence and characteristics of mental and behavioral disorders among 26 children, 3-17 years of age, with Usher syndrome.

Results: Six of the 26 children were diagnosed with a mental or behavioral disorder (1 with schizophrenia and mild mental retardation, 1 with atypical autism and severe mental retardation, 1 with atypical autism and mild mental retardation, 1 with mild mental retardation, and 2 with conduct disorder). Another 3 children had had a mental or behavioral disorder previously in their childhood.

Conclusion: Even though vision impairment first manifests in late childhood, some children with Usher syndrome seem to develop mental and behavioral disorders during childhood. The aetiology and treatment of mental and behavioral disorders among children with Usher syndrome are discussed. Children with Usher syndrome and their parents may need clinical support during early childhood to prevent development of mental and behavioral disorders.

Keywords: Deafblindness, Dual sensory loss, Mental and behavioral disorders, Usher syndrome, Psychiatry

American Journal of Medical Genetics Part A 143A:1560–1566 (2007)

Additional Clinical Manifestations in Children With Sensorineural Hearing Loss and Biallelic *GJB2* Mutations:
Who Should Be Offered *GJB2* Testing?

Margaret A. Kenna,[1,2]* Heidi L. Rehm,[1,3] Caroline D. Robson,[4] Anna Frangulov,[1] Jennifer McCallum,[5] Dinah Yaeger,[5] and Ian D. Krantz[5,6]

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Case study 3

Etiology may or may not be related to other disabilities

Etiology may not protect a child from other reasons for developmental conditions

Just a few examples from my clinical experiences:

- Branchio-oto-renal and XXYY
- GJB2 and Beckwith-Weidemann syndrome (associated with increased risk of tumor)
- GJB2 and Landau-Kleffner syndrome
- GJB and Branchio-oto-renal

"A dog that itches can have ticks and fleas"