Genetics of Hearing Loss

2013 Updates
Definitions

- **Hearing loss**
  - any degree of impairment of the ability to apprehend sound

- **Deaf**
  - people with profound hearing loss such that they cannot benefit from amplification

- **Hard of hearing**
  - mild to severe hearing loss but who can benefit from amplification.
Basic Components of Hearing

- Pinna (ear)
- External auditory canal
- Tympanic membrane
- Ossicles
  - malleus, incus, stapes
- Cochlea
- Semicircular canals
- Eighth cranial (auditory) nerve
Inner Ear

- Cochlea
  - Normal = 2 ½ turns
- Oval and round windows
  - Stapes pushes on oval window
  - As the stapes pushes oval window in, the round window bulges out
Organ of Corti

- The organ of Corti has highly specialized structures that respond to fluid-borne vibrations in the cochlea with a shearing vector in the hairs of some cochlear hair cells.

- It contains between 15,000-20,000 auditory nerve receptors. Each receptor has its own hair cell.
Organ of Corti

- The shear on the hairs opens non-selective transduction ion channels that are permeable to potassium and calcium.
- This leads to:
  - Hair cell plasma membrane depolarization
  - Activation of voltage-dependent calcium channels at the pole of the cells
  - This triggers vesicle exocytosis and liberation of glutamate neurotransmitter to the synaptic cleft
  - With resultant electrical signaling to the auditory cortex via spiral ganglion neurons.
The Organ of Corti

from WE Brownell, PhD,
"How the Ear Works: Nature's Solutions for Listening"
Homology

- There is a strong embryologic link between the ears and the kidneys
Parameters of Hearing

Audiogram

- A standard way of representing a person's hearing loss
- Most audiograms cover the limited range 100 Hz to 8000 Hz (8 kHz) which is most important for clear understanding of speech
- They plot the threshold of hearing relative to a standardised curve that represents 'normal' hearing, in dBHL
Parameters of Hearing

Oto-acoustic emission (OAE)

- Otoacoustic emission (OAE) measures an acoustic response that is produced by the inner ear, which in essence bounces back.

- The primary purpose of otoacoustic emission (OAE) tests is to determine cochlear status, specifically hair cell function.
Parameters of Hearing
Auditory Brainstem Response

- An ABR measures your brain's response to sound.
- It uses electrodes placed in strategic locations on the head to determine how well your acoustic nerve transmits the signal representing sound from the cochlea to the brain.
- The effects of sounds played into the ear can be measured as signals detected by the electrodes and provide insight into how well your whole hearing mechanism is working.
Parameters of Hearing
CT scan of temporal bone
Descriptive Classification of Hearing Loss

- Heritable / non-heritable
- Conductive / neurosensory / mixed
- Unilateral / bilateral
- Symmetric / asymmetric
- Congenital / acquired
- Progressive / stable / fluctuant
- Isolated / syndromic
Epidemiology and Etiology
Epidemiology

- All newborns
  - 1-2 / 1000
- NICU babies
  - 1-2/200
DeClau et all 2008

- ~87,000 NBS
- 170 + screen
- 116 confirmed permanent loss
  - 91 males, 79 females
  - 68 (58.6%) bilateral, 48 (41.4% unilateral)
  - 55.8% no identified risk factors
  - Etiology identified in 56%
Of those etiology identified:

- GENETIC (60.4%)
  - 13.8% Familial
  - 12.6% connexin 26
  - 4.6% chromosomal
  - 5.0% craniofacial malformation
  - 2.3% syndromic
Of those etiology identified:

- **PERI PARTAL (20.8%)**
  - HIE / asphyxia (3.4%)
  - Meningitis (1.1%)
  - Ototoxic drugs (2.8%)
  - Cerebral hemorrhage (3.4%)
  - ABO incompatibility (2.3%)
Of those etiology identified:

- TERATOGENIC (11.1%)
  - 10.3% CMV
  - 1.1% FAS
Etiology of Congenital Deafness

- recessive: 42%
- dominant: 12%
- X-linked: 4%
- other genetic: 2%
- non-genetic: 40%
I. NON-GENETIC HEARING LOSS
Etiology of Congenital Deafness

- 40% of deafness is “non-genetic”
  - teratogens
  - congenital/perinatal infections
  - hyperbilirubinemia
  - low birthweight
  - prematurity
  - NICU, ventilation
  - ototoxic medications
  - meningitis
Hearing Loss and Congenital Cytomegalovirus

- Reports of Mondini malformations and temporal bone dysplasia (congenital)
- Hearing loss may be progressive, not congenital
  - Mechanism = (?) labyrinthitis.
- Only certain way to diagnose is by titers in the immediate neonatal period.
  - Possibility to do DNA screening on newborn blood spots
CMV Infections

- 80% of children by 2 years old
- 90% of adults
- Therefore limited benefit of measuring titers
  - Helpful information only if negative
  - Rationale for NBS for CMV
Congenital Cytomegalovirus

- CNS changes
  - Microcephaly
  - Intracranial calcifications
  - Mental retardation
  - Cerebral palsy

- Optic atrophy, retinopathy, cataracts, microphthalmia

- Neurosensory hearing loss
  - may be the only manifestation

- Primary infection occurs in 2-4% of pregnancies
- Virus crosses placenta 30 - 40% of the time
  - about 1% (range 0.5 – 2.5%) of infants congenitally infected with CMV

- Hearing loss occurs in 8-12% of those prenatally infected

- Therefore 0.05 – 0.2% of all newborns are predicted to have CMV related hearing loss

- In the US about 5000 newborns per year have CMV related hearing loss
  - (may be the most common identifiable cause)
Fetal Alcohol Spectrum Disorders

- How common are they?
  - Alcohol related birth defects are the most common cause of MR, LD, SLD
  - An estimated 1/3 of all neurodevelopmental disabilities could be prevented by eliminating alcohol exposures
Fetal Alcohol Syndrome

- Limb abnormalities
- Crease differences
- Cardiac
- Small genitalia
- Ocular
- Skeletal
- Auditory
  - (25-30% of children with FAS have NSHL)
  - Overall incidence of newborn hearing loss secondary to FASDs unknown)
II. GENETIC HEARING LOSS
Etiology of Congenital Deafness

- 70% of genetic deafness is isolated
- 30% is complex
  - Other congenital anomalies
  - Dysmorphic features
  - NDD / NBD
  - Recognized syndromes, sequences, associations
A. Non-Syndromic, Monogenic Heritable Hearing Loss

- DFN = deafness
  - A = dominant (64 loci)*
  - B = recessive (98 loci)*
  - ( ) or X = X-linked (8 loci)
  - (e.g. DFNB1 = recessive hearing loss gene #1)
- Over 750 ‘associated genes’

*OMIM search 2013: Non-syndromic Hearing Loss DFNA64
Non-syndromic Hearing Loss DFNB98
AR - NSHL

- Usually congenital (pre-lingual)
- Usually severe to profound (exceptions = DFN B8 & DFN B13)
- 50% are DFN B1 (connexin 26)
Connexin 26 (DFNB1 / GJB2)

- Phenotype
  - non-syndromic
  - normal vision and vestibular function
  - non-progressive (2/3)
  - hearing loss = mild to profound with intra- and inter- familial variability
  - few kindreds are progressive and asymmetric

- Gene mapped to 13 q12
- 2 common mutations = 10% all pre-lingual deafness:
  - 35delG (85% N. Europeans)
  - 167delT (Jewish)
- 1 allele causes dominant deafness (DFNA3)
Compound Heterozygosity (Digeneic Inheritance)

- CX 26
- Hearing loss

- CX 30
- Hearing loss

- CX 26
- Hearing loss

- CX 30
AD - NSHL

- Usually post-lingual
- Usually progressive (onset in 2nd or 3rd decades)
DFNA1 (HDIA1)

- 5 q 31
- DIAPH (Homologue to *Drosophila* HDIA1 gene)
- Member of formin gene family
- Protein involved in regulation of actin polymerization in hair cells of the inner ear
“Progressive mixed deafness with fixed stapes and perilymphatic gusher”

- The stapes footplate is fixed in position, rather than being normally mobile. Results in a conductive hearing loss.
- A communication between the subarachnoid space in the internal auditory meatus and the perilymph in the cochlea, leading to perilymphatic hydrops and a 'gusher' if the stapes is disturbed.
  - Gusher often found during stapes surgery - contraindicated!
DFNX2

- This disorder is the result of mutations in the POU3F4 gene
  - (encodes a transcription factor)
- Protein function appears to be the regulation of mesenchymal fibrocytes
### Examples of Single Genes as Causes of Hearing Loss

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFNA1</td>
<td>DIAPH</td>
<td>Regulation of actin polymerization in hair cells of the inner ear</td>
<td>Abnormal actin</td>
</tr>
<tr>
<td>DFNB1</td>
<td>Connexin 26/GJB2</td>
<td>Facilitated rapid ion transport by-passing membrane diffusion</td>
<td>Disrupted ion transport</td>
</tr>
<tr>
<td>DFNB2</td>
<td>MYO7A</td>
<td>An unconventional myosin expressed only in the Organ of Corti. Bridges the sterocilia to the extracellular matrix</td>
<td>Abnormal anchoring of cilia</td>
</tr>
<tr>
<td>DFNX2 (X-linked perilymphatic gusher with fixed stapes)</td>
<td>POU3F4</td>
<td>Transcription factor</td>
<td>Regulation of mesenchymal fibrocytes</td>
</tr>
</tbody>
</table>
B. Syndromic Hearing Loss
Primary Hearing Loss Syndromes

- Alport
- Branchial-Oto-Renal
- Jervell and Lange-Nielsen
- Neurofibromatosis type 2
- Pendred
- Waardenburg
Jervell and Lange-Nielsen Syndrome

- AR
- Profound congenital deafness
- Syncopal attacks / sudden death due to prolonged QT
- High prevalence in Norway
J-L-N Family History

- Fainting
- Long QT
- Sudden death
- JLN
Jervell and Lange-Nielsen Syndrome

- Mutations are in one of two genes that co-assemble in a potassium channel (KCNQ1, KCNE1)
- Disrupts endolymph production in the stria vascularis
- Alleles in KCNQ1 produce isolated long QT syndrome
  - AD or AR
  - (3 other genes may also produce long QT)
### Hearing Loss Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gene function</th>
<th>Hearing loss features</th>
<th>Major non-hearing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alport syndrome</td>
<td>Collagens 4A3, 4A4 or 4A5</td>
<td>Basement membrane protein</td>
<td>Bilateral, sensorineural, high frequency, childhood onset, progressive</td>
<td>Glomerulonephritis with kidney failure</td>
</tr>
<tr>
<td>Branchio-oto-renal syndrome</td>
<td>EYA1</td>
<td>Regulation of genes coding for growth and development of embryo</td>
<td>Can be sensorineural, conductive or mixed. Often asymmetric. Mild to profound.</td>
<td>Malformations of the ears, kidneys and branchial arch derivatives</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen syndrome</td>
<td>KCNQ1, KCNE1</td>
<td>Potassium channel</td>
<td>Congenital, bilateral sensorineural</td>
<td>Cardiac conduction problems (long QT). May have fainting spells or sudden death</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Gene</td>
<td>Gene function</td>
<td>Hearing loss features</td>
<td>Major non-hearing features</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2 (merlin)</td>
<td>Regulates cell to cell communication and proliferation</td>
<td>Sensorineural hearing loss due to vestibular schwannomas</td>
<td>Nervous system tumors (neurofibromas, retinal hamartoma, meningiomas, gliomas)</td>
</tr>
<tr>
<td>Pendred syndrome</td>
<td>SLC26A4</td>
<td>Specific transporter of iodine</td>
<td>Congenital, bilateral sensorineural</td>
<td>Thyroid dysfunction due to defect in iodine trapping</td>
</tr>
</tbody>
</table>
C. Mitochondrial Hearing Loss

Trait 1: Mitochondrial myopathy

- Affected
- Carrier

I
- Affected

II
- Carrier

I
- Carrier

III
- Carrier

lactic acidosis, seizures
Isolated Mitochondrial Hearing Loss

- 12S rRNA gene mutation
  - A1555G confers a sensitivity to aminoglycosides (makes the RNA more similar to bacterial RNA)
  - A1555G also can be seen in maternally transmitted hearing loss
Mitochondrial Syndromes with Hearing Loss

- Diabetes - deafness
  - A3243G mutation in tRNA\textsuperscript{leu} (UUR)
  - hearing loss after onset of diabetes

- MELAS
  - mitochondrial encephalomyopathy, lactic acidosis, strokes, short stature
  - 30% NSHL
  - same mutation as diabetes - deafness
## Mitochondrial Disorders with Hearing Loss Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mitochondrial genetic changes</th>
<th>Hearing loss features</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside induced hearing loss</td>
<td>A1555G</td>
<td>Bilateral, high frequency hearing loss after aminoglycoside exposure</td>
<td>Increased risk may also be associated with noise induced hearing loss</td>
</tr>
<tr>
<td>Diabetes-deafness</td>
<td>A3243G</td>
<td>Sensorineural hearing loss (later onset, usually after diabetes)</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>MELAS</td>
<td>A3243G (same as diabetes deafness)</td>
<td></td>
<td>Encephalomyopathy, lactic acidosis, stokes, short stature</td>
</tr>
</tbody>
</table>
## Mitochondrial Disorders with Hearing Loss Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mitochondrial genetic changes</th>
<th>Hearing loss features</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-syndromic</td>
<td>A 1555G (same as aminoglycoside sensitivity)</td>
<td>Bilateral sensorineural</td>
<td>“Maternally transmitted hearing loss”</td>
</tr>
<tr>
<td>Non-syndromic</td>
<td>T7445C</td>
<td>Bilateral sensorineural</td>
<td>May have palmo-plantar keratosis</td>
</tr>
<tr>
<td>Pearson syndrome</td>
<td>Contiguous deletion / duplication of multiple mitochondrial genes</td>
<td>Congenital bilateral sensorineural</td>
<td>Failure to thrive, pancreatic dysfunction, metabolic acidosis, renal Fanconi syndrome, anemia, diabetes mellitus, early death</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>CISD2 (nuclear gene that regulates mitochondria)</td>
<td>Bilateral sensorineural</td>
<td>Diabetes mellitus, diabetes insipidus, optic atrophy, retinal dystrophy</td>
</tr>
</tbody>
</table>
Mitochondrial Genes in Hearing Loss

- Presbycusis
  - hearing loss associated with aging
  - accumulation of mtDNA mutations
III. HEARING LOSS WITH VISUAL ANOMALIES
Hearing Loss with Visual Problems

- Usher syndrome
- Wolfram syndrome (DIDMOAD)
- Norrie disease
- Mitochondrial disorders
Usher Syndrome (s)

- Association of hearing loss with retinitis pigmentosa
- At least 11 loci
- 2 identified
## Hearing Loss Syndromes also with Visual impairments

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gene function</th>
<th>Hearing loss features</th>
<th>Visual features</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfram syndrome</td>
<td>WFS1, CISD2,</td>
<td>Endoplasmic reticulum function</td>
<td>Bilateral sensorineural hearing loss. Onset early adulthood</td>
<td>Optic atrophy, retinal dystrophy, ptosis</td>
<td>Diabetes mellitus, diabetes insipidus</td>
</tr>
<tr>
<td>Norrie disease</td>
<td>NDP (norrin)</td>
<td>Growth factor</td>
<td>Bilateral sensorineural hearing loss. Onset early adulthood</td>
<td>Retinal dysplasia / dysgenesis, cataracts, optic atrophy, malformations of globe and anterior chamber</td>
<td>Mental retardation, epilepsy, dementia</td>
</tr>
<tr>
<td>Usher syndrome(s)</td>
<td>Marked heterogeneity with 12 loci identified thus far</td>
<td>Multiple</td>
<td>Mild to profound, bilateral sensorineural loss</td>
<td>Retinitis pigmentosa</td>
<td>Vestibular dysfunction, subtle CNS involvement</td>
</tr>
</tbody>
</table>
IV. PRIMARY ACOUSTIC MALFORMATIONS

- Aural atresia
- Middle ear atresia
- Cochlea / inner ear
  - Michel
    - complete aplasia of inner ear structures
  - Mondini
    - 1 1/2 turns of cochlea, dysplasia of apex
  - Enlarged vestibular aqueduct
Enlarged Vestibular Aqueduct
V. Types of Hearing Loss

Genes

- Ion channels / transport
- Connective tissue proteins
- Ear ‘muscles’
- Embryogenic influences
- Transcription factors
- Protein synthesis
- Cellular communication
- Energy metabolism
- Susceptibility to environmental damage
- Growth factors
VI. Genetic Evaluation Of Hearing Loss

Once hearing loss is identified, what are the steps in determining the cause?
Testing for the Etiology of Newborn Hearing Loss

- Potentially 25% are congenital CMV or Connexin 26 related
# Medical Genetic Evaluation of Hearing Loss

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Genetics</td>
<td>Vestibular</td>
</tr>
<tr>
<td>Audiology</td>
<td>Ophthalmology</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>CT of temporal bones</td>
</tr>
<tr>
<td></td>
<td>Urinalysis/serum creatinine</td>
</tr>
<tr>
<td></td>
<td>Serology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perchlorate discharge (if CT abnormal)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Electroretinogram</td>
</tr>
<tr>
<td>DNA</td>
</tr>
</tbody>
</table>
Non-Syndromic Hearing Loss

Connexin Testing (GJB2 & ΔGJB6-D13S1830)

Connexin Negative/Heterozygous

Family History

Mitochondrial
- Mixed/SNHL +/− perilymphatic gusher
  - Mitochondrial Panel
    - reflex
    - OtoChip

X-linked
- Low Freq. SNHL
  - POU3F4

Dominant
- Late onset SNHL w/ vestibular symptoms
  - COCH
    - reflex
    - OtoChip
- No defining features
  - OtoChip

Recessive/Sporadic
- Auditory neuropathy/dysynchrony
- EVA +/− Mondini dysplasia
- No defining features
- +/− Retinitis Pigmentosa/abnl ERG
  - SLC26A4 (PDS)/BOR eval
  - OtoChip
  - OtoChip

Usher Syndrome

No Family History

History of Aminoglycosides
The Medical Genetic Evaluation

Medical History
  Prenatal, birth, developmental histories
Family History
  Pedigree construction and analysis
Physical Examination
  Physical findings, dysmorphic features
Diagnosis
Genetic Counseling
  Interpretation of results
Medical History

- Co-morbid medical conditions
- Procedures, hospitalizations
- Structural congenital anomalies
- Neurodevelopmental disorders
- Neurobehavioral disorders
Family History

For each family member:
Is there hearing loss?
Type?
Age of onset?
Progression?
Known cause?
Are there related conditions?
Physical disabilities?
Medical problems?
Dysmorphic features?
Need to know the right questions!
Physical Examination

Growth
  height, weight, head circumference

Dysmorphology
  shape, size, position of features
  minor variations
  can be very subtle
Molecular Genetic Evaluation of Hearing Loss

For gene testing to be practical:

• The gene must be known
• It should be small
• There should be one or a few very common mutations
• The prognosis should be consistent

Examples:

Connexin 26 (GJB2)
small gene, one very common mutation in Caucasians, one in Ashkenazi Jews, one in Asians

Pendred syndrome/DFNB4 (PDS)
fairly small gene, 4 fairly common mutations account for 70%

Stickler syndrome (COL2A1)
huge gene, many mutations cost >$1500
Genetic Testing Options

- Chromosomal analysis (karyotype)
- Single locus FISH
- Targeted mutation analysis
- Array based comparative genomic hybridization (aCGH)
  - General, clinical
  - Hearing loss specific
- Gene sequencing
  - Single gene sequencing
  - High-throughput sequencing panel
  - Nextgen sequencing
    - Exome
    - Genome
### OtoChip: Gene Specific Clinical Information

<table>
<thead>
<tr>
<th>Gene</th>
<th>Age of Onset</th>
<th>Progressive</th>
<th>Severity</th>
<th>Audiogram Shape/Frequency</th>
<th>Vestibular</th>
</tr>
</thead>
<tbody>
<tr>
<td>GJB2</td>
<td>AR: Congenital to childhood&lt;br&gt;AD: Congenital to late onset</td>
<td>Yes, in some</td>
<td>AR &amp; AD: MILD to profound&lt;br&gt;AR &amp; AD: Variable, mainly flat or sloping</td>
<td>Typically normal</td>
<td></td>
</tr>
<tr>
<td>GJB6 (sequencing only)</td>
<td>Congenital to early childhood</td>
<td>Yes, in some</td>
<td>Mild to profound</td>
<td>Typically normal</td>
<td></td>
</tr>
<tr>
<td>MTNR1 (mitochondrial)</td>
<td>Congenital to late onset</td>
<td>Yes</td>
<td>Mild to profound</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>MTTS1 (mitochondrial)</td>
<td>Congenital to late onset</td>
<td>Yes</td>
<td>Mild to profound</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>MYO6</td>
<td>AR: Congenital&lt;br&gt;AD: Postlingual</td>
<td>Yes</td>
<td>AR: Severe to profound&lt;br&gt;AD: Mild to profound</td>
<td>All frequencies</td>
<td></td>
</tr>
<tr>
<td>OTOF</td>
<td>Congenital</td>
<td>No</td>
<td>Severe to profound AN/AD</td>
<td>Abnormal in some</td>
<td></td>
</tr>
<tr>
<td>SLC26A4 (PDS)</td>
<td>AR/Pendred: Congenital</td>
<td>Yes</td>
<td>Severe to profound</td>
<td>Abnormal in some</td>
<td></td>
</tr>
<tr>
<td>TMC1</td>
<td>AR: Congenital&lt;br&gt;AD: Postlingual</td>
<td>Yes</td>
<td>AR: No&lt;br&gt;AD: Yes</td>
<td>All frequencies</td>
<td>Unknown</td>
</tr>
<tr>
<td>TMIE</td>
<td>Congenital</td>
<td>No</td>
<td>Severe to profound</td>
<td>All frequencies</td>
<td>Normal</td>
</tr>
<tr>
<td>TMPRSS3</td>
<td>Congenital to postlingual</td>
<td>Yes, in some</td>
<td>Severe to profound</td>
<td>All frequencies</td>
<td>Normal</td>
</tr>
<tr>
<td>MYO7A</td>
<td>AR/Usher 1: Congenital&lt;br&gt;AD: Postlingual</td>
<td>Yes, in some</td>
<td>AR/Usher: All frequencies&lt;br&gt;AD: Variable</td>
<td>Typically abnormal</td>
<td></td>
</tr>
<tr>
<td>USH1C</td>
<td>AR/Usher 1: Prelingual</td>
<td>No</td>
<td>Severe to profound</td>
<td>All frequencies</td>
<td>Unknown</td>
</tr>
<tr>
<td>CDH23</td>
<td>AR/Usher 1: Congenital</td>
<td>Yes, in some</td>
<td>Moderate to severe</td>
<td>All frequencies</td>
<td>Normal</td>
</tr>
<tr>
<td>PCDH15</td>
<td>AR/Usher 1: Congenital</td>
<td>Yes, in some</td>
<td>Moderate to severe</td>
<td>All frequencies</td>
<td>Abnormal</td>
</tr>
<tr>
<td>USH1G (SANS)</td>
<td>Usher 1: Congenital</td>
<td>No</td>
<td>Profound</td>
<td>All frequencies</td>
<td>Abnormal</td>
</tr>
<tr>
<td>USH2A</td>
<td>AR/Usher 1: Prelingual onset&lt;br&gt;ARRP: No HL</td>
<td>Yes, in some</td>
<td>Moderate to profound&lt;br&gt;High frequency (sloping)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>GPR98 (VLGR1)</td>
<td>Usher 2: Prelingual onset</td>
<td>Yes, in some</td>
<td>Moderate to severe&lt;br&gt;High frequency (sloping)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>DFNB31 (WHRN)</td>
<td>Usher 2: Prelingual onset</td>
<td>Yes, in some</td>
<td>Moderate to severe&lt;br&gt;High frequency (sloping)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>CLRN1 (USH3A)</td>
<td>Usher 3: Variable, congenital to 40s</td>
<td>Yes</td>
<td>Moderate to severe&lt;br&gt;Variable</td>
<td>Abnormal in some</td>
<td></td>
</tr>
</tbody>
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**OtoChip™ Test**

**For Hearing Loss and Usher Syndrome**

**Background:**

Hearing loss is the most common sensory impairment with an incidence of 1 in 1,000 newborns. There are currently over 100 genes identified to cause hearing loss. The OtoChip™ test is designed to identify mutations in these genes that are associated with hearing loss. The test uses a highly sensitive and specific method to detect mutations that cause hearing loss. The test is performed on DNA extracted from blood or saliva, and results are available within 2-4 weeks.

The OtoChip™ test includes analysis of over 100 different genes associated with hearing loss. The test results provide information on the most likely cause of hearing loss, as well as any potential genetic counseling implications.

**Genes Analyzed:**

- **Non-syndromic autosomal recessive:***
  - Usher syndrome types 1A, 1B, 2A, 2B, 3A, 3B
  - Pendred syndrome
  - Deafness, autosomal recessive, early-onset, non-syndromic
  - Deafness, autosomal recessive, late-onset, non-syndromic

- **Non-syndromic autosomal dominant:**
  - Usher syndrome types 1C, 1D, 1E
  - Pendred syndrome
  - Deafness, autosomal dominant, non-syndromic

- **Mitochondrial:**
  - Usher syndrome types 1F, 1G
  - Pendred syndrome

- **Auditory neuropathy:**
  - Usher syndrome types 1I, 1J

**Purpose:**

The OtoChip™ test is designed to help identify the underlying cause of hearing loss in individuals. The results provide valuable information for genetic counseling and treatment options.

**Contact Information:**

If you have any questions, please call the Laboratory for Molecular Medicine at 888-788-5280 or email us at UoBF@partners.org.
The first truly comprehensive genetic test for hereditary hearing loss, Usher syndrome and Pendred syndrome.

| What is OtoSCOPE? | How to order OtoSCOPE | Genes Included on OtoSCOPE |

**Genes Included On OtoSCOPE®**

**AUTOSOMAL RECESSIVE NON-SYNDROMIC DEAFNESS GENES:** CDH23, CLDN14, COL11A2, ESPN, ESRRB, GIPC3, GJB2, GJB3, GJB6, GPSM2, GRXCR1, HGF, ILDR1, LHFPL5, LOXHD1, LRTOMT, MARVELD2, MYO3A, MYO6, MYO7A, MYO15A, OTOA, OTOF, PCDH15, PJVK, PTRQ, RDX, SLC26A4, SLC26A5, STRC, TECTA, TMC1, TMIE, TMPRSS3, TPRN, TRIOBP, USH1C, WHRN

**AUTOSOMAL DOMINANT NON-SYNDROMIC DEAFNESS GENES:** ACTG1, CCDC50, COCH, COL11A2, CRYM, DFNA5, DIAPH1, DSPP, EYA4, GJB2, GJB3, GJB6, GRHL2, KCNQ4, MYH14, MYH9, MYO1A, MYO6, MYO7A, POU4F3, SLC17A3, TECTA, TMC1, TJP2, WFS1

**X-LINKED NON-SYNDROMIC DEAFNESS GENES:** POU3F4, PRPS1

**MICRO-RNAS AND MITOCHONDRIAL GENES:** miR-96, miR-182, miR-183, MT-RNR1, MT-TS1

**PENDRED SYNDROME GENES:** SLC26A4

**USHER SYNDROME GENES:** CDH23, CLRN1, GPR98, MYO7A, PCDH15, USH1C, USH1G, USH2A, WHRN
Predefined Disease or pathway Genes

Cancer, Deafness, Heart Disease, ADME genes.... NGS of selected targets allows high coverage

Human & Mouse Exome NGS

Lowest Price on the market for human exome sequencing. Guaranteed! $698 for the 1st sample.

Epigenetic Profiling Services

Genome-wide profiling of epigenetically modified DNA for cancer and stem cell biology, and more.

Custom Targeted NGS sequencing

You provide gene target lists, we will capture & sequence up to 20M bps. Starting from $1,280/sample

RNA-Seq

Digital Gene Expression

High-quality RNA-Seq (~$698/sample) at a cost less than the microarrays, and can do much more
Whole Exome Sequencing
Clinical Application

- Currently whole exome sequencing is available as a clinical test.
- Over the past year we have been able to negotiate:
  - Costs down to $4500 for singleton cases
  - Turn around times of 3-4 months
- Third party coverage is cumbersome
- Early successes in selected cases
- Huge issue with data culling
Interpretation of Results of Molecular Testing

If positive:
what is the prognosis? Is there variation in expression or penetrance?

If negative:
How many different genes were tested?
How was the test done? Only common mutations or the whole gene?

undiscovered mutations may still exist
Negative DNA testing does not mean that the cause is not genetic
Summary

Genetic Diagnosis is important for prognosis, management, and counseling.

Clinical evaluation is done through a combination of physical examination, family history, and medical / genetic tests.
Q: In a newborn with hearing loss - which sample should be tested for cmv - urine or blood?
A: Ideally, both. A positive culture in a newborn gives a definite diagnosis. Virus in the urine becomes less likely to be found as the infant grows older. Later, titers are all that is needed.

Q: I just identified a 29 day old with severe loss, and rx’d to PCP will test urine. Is that too late and should blood spot be used?
A: By this age, titers would be best.

Q: I have a student diagnosed with auditory neuropathy and has gotten bilateral cochlear implants and is now diagnosed with OPA1 Dominant Optic Atrophy. How does this typically affect vision?
A: Optic atrophy produces vision loss. How much and if it progresses are dependent on the cause. In a child with OA and auditory neuropathy, a genetic cause is likely. The child should have a full genetics evaluation to help determine this.

Q: 5000 newborns per year have CMV related hearing loss, why are we not screening for CMV at birth by saliva testing?
A: Mainly there are practical issues in mass screening that have not been successfully worked out.

Q: Do you feel isolated unilateral microtia, with canal atrieia and HL, is in the spectrum of craniofacial microsomia (and Goldenhar's)
A: Absolutely

Q: Genetic testing for isolated microtia?
A: None yet