Genetic Causes of Hearing Loss

Hearing Loss is the Most Common Congenital Anomaly

Major Causes of Hearing Loss

DNA is Highly Compacted into Chromosomes

Genes are found on chromosomes

Human Karyotype
We inherit two copies of each chromosome (and each gene), one from each parent.

Chromosome Abnormalities

Trisomy 21 (Down’s Syndrome)

How is hearing loss inherited?

Autosomal Dominant Inheritance

Some forms of hearing loss are caused by only one copy of a mutated gene.

This hearing loss is seen in every generation.

If a parent has a dominant mutation, each child has a 50% chance of inheriting it.

Dominant hearing loss is more often seen with later-onset forms of genetic hearing loss.

Hearing Loss

Autosomal Recessive Inheritance

The majority of childhood hearing loss is recessive, meaning both copies of a gene must have variants.

Often, there is no family history of hearing loss.

Each child will have a 25% chance of having hearing loss.

A carrier is a person who carries one copy of a recessive mutation, but does not have hearing loss.

X-Linked Inheritance

Only males have hearing loss.

Each son will have a 50% chance of having hearing loss.

Each daughter has a 50% chance of being a carrier.

Example: POU3F4

Hearing Loss

Carrier

Carrier
Mitochondrial Inheritance

Only the mother passes mitochondria to her children.

All children will inherit a mitochondrial variant from their mother.

Mitochondrial hearing loss is often variable in its age of onset, severity and progression.

Examples:
- 12S rRNA (MTRNR1)
- tRNAserUCN (MTTS1)

Genetic Testing

What is it?
Determine whether you have a mutation (variant) in a gene which can result in a trait such as hearing loss.

What can be tested?
- Metabolic substances (e.g. PKU)
- Proteins (e.g. IRT for Cystic Fibrosis)
- Chromosomes (e.g. Down’s Syndrome)
- Genes (e.g. Connexin 26)

All of these are tested using a blood sample.

How is genetic testing done?
- Physician (ENT, PCP, pediatrician, geneticist) or genetic counselor discusses testing with the patient/family and they decide to order genetic testing
- Blood sample is obtained (sometimes saliva or cheek brushes can be used) and sent to the lab by overnight mail
- Testing is completed and report written
- Lab returns report to physician
- Physician or genetic counselor communicates results to patient
- If positive, family member testing becomes available for identified variants for a fraction of full test cost

DNA Testing

Normal DNA Sequence
ATGG TG CCT CAGG AT

DNA Sequence with Variant
ATGG TG CCT TAGG AT

Nonsyndromic Deafness Genes in the Human Genome

50/135 Genes Identified

Major Causes of Hearing Loss

- Traumas/Exposures
- Infections
- Drugs
- Unknown

Genetic
- Syndromic
- Non-syndromic
- Autosomal Dominant
- Autosomal Recessive
- Mitochondrial
- X-Linked

Cx26
**GJB2 - Connexin 26**

**DFNB1 (Recessive) Mutations**
- Splice Site: IVS1+1G>A

**DFNA3 (Dominant) Mutations**
- delE42, W44S/C, R75Q, D179N, R184Q, C202F, M163L
- w/ Skin Disease: G12R, S17F, D50N, N54K, G59A, D66H, R75W, R75Q

**Unknown Significance**

**Polymorphisms**

**Carrier Rates and Common Mutations**
- Caucasian: 2-3% (35delG common)
- Ashkenazi Jewish: 3-4% (167delT common)
- Asian: (235delC and V37I common)
- African American: (R143W may be common)

**Severity of Cx26 Hearing Loss**

**Progression of Cx26 Hearing Loss**

**Delayed Onset Cx26 Hearing Loss**
Norris et al. Ear Hear. 27(6):732-741, 2006. ~4% of Cx26 cases pass newborn hearing screens

**Base Deletion: Cx26 – 35delG**
- ...ACGATCCTGGGGGTGTG...normal
- ...ACGATCCTGGGGXTGTG...variant

**Anatomy of the Human Ear**

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Hair Cell Stimulation

Sound wave

Hair Cell Transduction


Connexin 26 Gap Junction

Metabolic Recycling in the Cochlea

Endolymph

Why is there only a small fraction of genetic tests available for hearing loss when over 50 genes have been identified?
Syndromic Hearing Loss

- **Syndromes**
  - Alport
  - Branchio-Oto-Renal
  - Jervell and Lange-Nielsen
  - Mitochondrial (MELAS/MERRF)
  - Neurofibromatosis type II
  - Norrie
  - Osteogenesis Imperfecta
  - Pendred
  - Stickler
  - Treanegrau-Mohr (DFN1)
  - Treacher Collins
  - Usher
  - Waardenburg

- **Gene(s)**
  - COL4A5, COL4A3, COL4A4
  - EYA1
  - KCNQ1, KCNE1/IsK
  - tRNAleu(UUR), tRNAlys
  - NF2
  - NDP
  - COL1A1, COL1A2
  - SLC26A4 (PDS)
  - COL2A1, COL11A2, COL11A1
  - DDP
  - TCOF1
  - MYO7A, USH1C, CDH23, PCDH15, SANS, USH2A, GPR98, USH3
  - PAX3, MITF, SLUG, EDNRB, EDN3, SOX10

There are currently over 400 syndromes with associated hearing loss.

Usher Syndrome Early Diagnosis

- **ERG and other ophthalmological exams** may not be positive until adolescence.
- **Vestibular assessment** (delayed motor milestones, VEMP, minimized rotation testing, caloric, rotary chair) – test methods are age dependent and not diagnostic for USH1 (not useful for USH2).
- Teschner 2007: 16.2% of deaf children had absent vestibular responses from a new “minimized rotation” test and 50% of them had abnormal ERGs.
- **Genetic testing**; not age dependent but may not have conclusive distinction between syndromic vs nonsyndromic prediction if performed early.

OtoChip for Hearing Loss and Usher Syndrome

- **Nonsyndromic**
  - Aminoglycosides
  - Mitochondrial
  - X-linked

- **Syndromic**
  - Family Hx
  - No Family Hx

- **Appropriate Gene(s)**
  - Mito
  - PDS
  - COCH
  - POU3F4
  - USH1

19 genes - 428 amplicons 68159 bases

Usher Syndrome Treatment

- **Vitamin A supplementation**
- **Sunglasses**

**Gene Therapy**: Acland et al. 2001 successful gene therapy for RP and LCA in dogs.
Hashimoto et al. 2007 MYO7A gene therapy in Usher mice.
Bainbridge et al. 2008 early human gene therapy trials for LCA.
Collaboration with Samuel Jacobson (UPenn): Recruiting positive MYO7A cases for visual function studies in anticipation of gene therapy trials.