GENETICS AND HEARING LOSS

Jennifer A. Defant, M.S., C.G.C.
Certified Genetic Counselor
Division of Genetics and Metabolism
University of Florida
CAUSES OF DEAFNESS:

- 60% of childhood hearing loss is genetic
  - Syndromic
  - Nonsyndromic

- 40% of childhood hearing loss is caused by infectious/environmental factors
  - Prenatal infections (CMV, toxoplasmosis, etc)
  - Meningitis
  - Low birth weight/prematurity
  - Oto-toxic medications
  - Mechanical ventilation
  - Trauma
60% of deafness is genetic

Genetic hearing loss

- Nonsyndromic, AR: 56
- Syndromic: 30
- Nonsyndromic, XL-mitochondrial: 12
- Nonsyndromic, AD: 2
Nonsyndromic hearing loss
- Categorized by mode of inheritance:
  - DFN - X-linked deafness (~1%)
  - DFNA - Autosomal dominant deafness (12%)
  - DFNB - Autosomal recessive deafness (56%)
  - Mitochondrially inherited deafness (~1%)

Syndromic hearing loss
- 300+ syndromes with deafness as component
Chromosomes in every cell
23 pairs of chromosomes for total of 46
One from each pair we inherit from mom and the other from dad
Chromosomes contain our genes
Modes of inheritance for non-syndromic hearing loss

Autosomal Dominant
DFNA – 12%

X-linked
DFN – 1%

Autosomal Recessive
DFNB – 56%

Mitochondrial
1%
Why is genetic deafness so common?

There are so many genes associated with hearing loss.
Genetic Evaluation of Deafness

- Complete family history, prenatal and medical history, developmental assessment and physical examination

- Associated testing may include:
  - EKG, audiologic and vestibular testing, ophthalmology exam, X rays, CT/MRI of inner ear
Hearing Loss Syndromes

- Account for 20-30% of genetic HL
- >300 syndromes
- Each syndrome is relatively rare
- Syndromes identified by:
  - Physical examination findings
  - Internal ear malformations
  - Physiological traits (e.g., ECG changes)
Pendred Syndrome

- Hearing loss, usually prelingual
- Goiter in 2nd decade, most are euthyroid
- Large vestibular aqueduct and endolymphatic sac
- Upper 2/3 of cochlea is poorly formed
CHARGE Syndrome
Coloboma of the iris or retina
Heart defects
Atresia or stenosis of the choanae
Retarded growth and development
Genital hypoplasia in males
Ear anomalies
Deafness and Pigmentation

- Neural crest cell migration in early embryonic development is critical to both hearing and pigmentation processes.
- Waardenburg syndrome and LEOPARD syndrome both involve defects in pigmentation and hearing loss.
Waardenburg syndrome

- Accounts for 2-3% of all congenital deafness
- Several types of Waardenburg syndrome, most common type I
- Autosomal dominant inheritance
- PAX3 (2q35) and MITF (3p1) genes implicated in WS-I and WS-2
Waardenburg syndrome

- White forelock
- Heterochromia irides
- Synophrys
- Telecanthus
- Nl intelligence
- Nl lifespan
LEOPARD Syndrome

- Autosomal dominant inheritance
- Gene same as gene for Neurofibromatosis type 1 (NF1)
LEOPARD Syndrome

- Lentigines
- EKG abnormalities
- Ocular hypertelorism
- Pulmonic stenosis
- Abnormal genitalia
- Retarded growth
- Deafness
Retinal Abn. and Deafness

- Retinal abnormalities seen in approx. 10% of deaf population
- Most commonly Retinitis Pigmentosa (RP - progressive night blindness)
- Usher syndrome, Refsum disease are autosomal recessive disorders and Norrie disease is X-linked recessive
- Suggest that all deaf individuals have ophthalmologic evaluations
Usher Syndrome

- Progressive night blindness due to RP
- Sensorineural hearing loss
- Eventual blindness and deafness
- Balance problems
- Multiple different genes can cause
Kidney Problems and Deafness

- Renal problems occur in a significant number of individuals with deafness.
- Primarily accounted for by 2 diseases: Alport syndrome and BOR syndrome.
- Suggested that all children with hearing loss have evaluation of kidney structure and function.
Alport syndrome

- Progressive hearing loss in teen age or early adult years
- Renal problems characterized by hematuria and proteinuria; sometimes leading to end-stage renal failure
- Inherited as X-linked dominant or autosomal recessive trait
- Gene testing available
Cardiac conduction defects and deafness

- Presence of prolonged QT and heart arrhythmia is known as “Long QT syndrome”
- When associated with SNHL results in a condition called Jervell-Lange-Nielsen
- JLN is inherited as an autosomal recessive condition, but heterozygotes display long QT intervals
- Genetic testing for JLN is available clinically - genes involved are KVLQ1 and KCNE1
Thyroid disease and deafness

- Goiter/thyroid dysfunction occurs in Pendred syndrome
- Most common genetic cause of deafness, accounting for 5% of deaf individuals
- PDS gene at 7q31 responsible for Pendred syndrome and some nonsyndromic hearing loss (DFNB4)
- Autosomal recessive inheritance
Other syndromes with SNHL

- Hundreds of other genes which result in SNHL with other physical findings
- Some of these conditions are very rare, others common
- Identification of SNHL genes continues at a fast rate, but the utility of genetic testing for many of these conditions is not keeping pace
Goldenhar syndrome

- Aka Hemifacial Microsomia
- Features include:
  - facial asymmetry
  - eye abnormalities (epibulbar dermoid)
  - ear malformations
  - vertebral anomalies
- Sporadic inheritance
TREACHER COLLINS SYNDROME

Features include:
- downslanting eyes
- eyelid colobomas
- dysplastic ears & conductive deafness
- small chin
- nl intelligence

- Autosomal dominant inheritance
- Gene testing available
Protocol for evaluation of childhood deafness

History, Physical Exam & Audiology evaluation

- Diagnosis Apparent
  - Treatment
    - Sev - Prof
      - C26 screen
        - +/+
        - +/-
        - +/- C30 screen
          - +/-
          - +/+
          - +/- Genetic Counseling
          - CT scan
          - EKG
          - Lab tests as appropriate
          - CT scan
          - EKG
          - Lab tests as appropriate
    - Mod - Sev
      - CT scan
      - EKG
      - Lab tests as appropriate
    - Mild - Mod
      - CT scan
      - EKG
      - Lab tests as appropriate
  - Diagnosis Unclear
    - CT Scan
    - Serial Audiograms
    - ? C26 screening
    - Bilateral
      - Treatment
      - CT scan
      - EKG
      - Lab tests as appropriate
    - Unilateral
Inherited in autosomal dominant, recessive, X-linked recessive and mitochondrial patterns

- DFN - X-linked (2-3%)
- DFNA - Autosomal dominant (10-20%)
- DFNB - Autosomal recessive (75-80%)
- Mitochondrial (< 1%)
Accounts for 10% of all hearing loss
Accounts for 30% of all sporadic deafness
Accounts for 50-80% of autosomal recessive hearing loss
Gene codes a gap junction in the cochlea (GJB2)
1/50 US Caucasians carry a mutation
Connexin 26 Clinical Features

- Hearing loss is prelingual
- Hearing loss is non-progressive
- Severity varies both between families and within a given family
- No health or learning problems associated
- Connexin 26 gene is implicated in KID syndrome (keratoderma, ichthyosis, deafness)
Gene codes a gap junction in the cochlea (GJB6)

Mutations can interact with mutations in Connexin 26 to result in recessive hearing loss

Accounts for 3% of all recessive hearing loss but is much more common in the Spanish population

May account for deafness in 30-70% of Connexin 26 heterozygotes
Genetic Counseling for NSHL

- Genetic testing is available for only a few of the genes which have currently been identified for NSHL.
- At present, genetic counseling very often consists of risk appraisal without the option of DNA testing or prenatal diagnosis by DNA or other methods.
- Advances in the field may result in rapid changes to what we are able to offer families.
Questions?