Genetic Hearing Loss

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Introduction

- Deafness affects 1.3-2.3 per 1000 children
- About 50% of childhood SNHL attributed to genetic factors, 20-25% environmental factors, and 25-30% sporadic
- Relative increase in prevalence of genetic SNHL mandates clinicians be familiar with the diseases
- Genetic syndromes usually classified by other involved systems
- Nonsyndromic HL characterized by audiologic characteristics, age of onset, presence or absence of progression, and mode on inheritance
- 75-80% of genetic deafness attributed to AR inheritance, 18-20% to AD, with the remainder classified as X-linked or chromosomal disorders
Basic Genetic Principles

- Human genes are arranged linearly on 22 pairs of autosomes and one pair of sex chromosomes
- Each chromosome carries a distinctive set of gene loci for which there may be several alleles
- The phenotype is determined by which alleles are present and how they interact
Autosomal Dominant Inheritance

- Vertical pattern of transmission
- 50% chance of affected heterozygote passing gene to children
- A new mutation in the gene resulting in the offspring being first affected and then may be inherited in a dominant fashion
- Dominant genes may exhibit lack of penetrance, which is an all or none phenomenon; either the gene is expressed or not expressed
- May show variable expressivity with different family members showing different manifestations of the trait
Autosomal Dominant Inheritance

**FIG. 89-1.** Autosomal-dominant inheritance. Vertical pattern of trait expression; males and females are equally affected.
Autosomal Recessive Inheritance

- Most common pattern of transmission in hereditary hearing loss
- 25% chance that offspring will be affected
- Characterized by horizontal pattern of affected individuals
- For offspring to have disorder, both parents must be carriers of the gene
Autosomal Recessive Inheritance

FIG. 89-2. Autosomal recessive inheritance. Horizontal pattern of trait expression. Parental consanguinity is often present in families with autosomal recessive disorders.
X-Linked Inheritance

- Involves particular genes located on the X chromosome
- Disorders more commonly affect males
- Heterozygote female will pass the gene to 50% of her sons who will express the trait, and to 50% of her daughters who will be carriers for the trait
- Affected males pass the gene to all of their daughters and none of their sons
- Hallmark is absence of male to male transmission
X-Linked Inheritance

FIG. 89-3. X-linked recessive inheritance. Males only are affected. There is no male-to-male transmission, and daughters of affected males are carriers.
Mitochondrial Inheritance

- Rare mode of inheritance for HHL
- Caused by a mutation in the small amount of DNA present in the mitochondria of cells
- Inherited only from the mother because sperm do not transmit mitochondria to the offspring
- Expression of hearing impairment varies between affected people because only a fraction of the mitochondria harbor the mutation
- Typical mitochondrial disorders gradually worsen
Mitochondrial Inheritance

FIG. 89-7. Mitochondrial inheritance. Inheritance follows the maternal line. Individuals can be either normal, heteroplasmic (both normal and mutated mtDNA), or homoplasmic (all mtDNA are mutated).
Gene Mapping and Localization

- Genetic linkage analysis is a process for determining precise chromosomal location.
- It takes advantage of crossover, where genetic material can be randomly exchanged during cell meiosis.
- Two genetic loci are said to be linked when they are close enough together on the chromosome that their alleles are transmitted together more often than expected by chance.
- Genetic heterogeneity implies that different mutations can result in an identical or similar phenotype.
Crossover

FIG. 93-4. Recombinante.
Gene Mapping and Localization

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Inner Ear Structural Malformation

- Cochlea fully formed by week 9 of gestation
- Arrest in development or aberrant development may lead to hearing loss
- 20% of children with congenital SNHL have subtle or severe abnormalities of the inner ear
- The deformities are classified into 5 different groups
Michel Aplasia

- Complete agenesis of petrous portion of temporal bone
- External and middle ear may be unaffected
- Thought to result from an insult prior to the end of the third gestational week
- Affected ears are anacusis
- Autosomal dominant inheritance has been observed
Mondini Aplasia

- Developmentally deformed cochlea where only the basal coil can be identified
- Interscalar septum is absent and endolymphatic duct is enlarged
- Thought to result from insult around the sixth week of gestation
- Can be inherited in AD fashion
- Also described in Pendred’s, Waardenburg’s, Treacher Collins, and Wildervaank’s syndromes
Scheibe Aplasia

- Also known as cochleosaccular dysplasia or pars inferior dysplasia
- Normal bony labyrinth and superior portion of membranous labyrinth
- Organ of Corti is poorly differentiated with deformed tectorial membrane and collapsed Reissner’s membrane
- Most common form of inner ear aplasia
- Can be inherited as AR
Alexander Aplasia

- Limited cochlear duct differentiation at the level of the basal coil
- Has resultant effects on organ of Corti and ganglion cells
- See high frequency hearing loss
Enlarged Vestibular Aqueduct

- Has been associated with early onset SNHL, usually progressive and bilateral
- Progressive HL is the result of hydrodynamic changes and possible labyrinthine membrane disruption
- Abnormality may also accompany cochlear and SCC deformities
- Familial cases suggest AD inheritance; AR inheritance is also possible
- Has been associated with Pendred’s syndrome
Semicircular Canal Malformations

- Canal formation begins in the sixth gestational week
- Superior canal is formed first and lateral canal is the last to be formed
- Isolated lateral canal deformities are the most commonly identified inner ear malformation on CT scans
- Superior canal deformities are always accompanied by lateral canal deformities whereas lateral canal deformities often occur in isolation
Classification of HHI

- Syndromic and nonsyndromic forms
- Up to 30% due to syndromic forms
- Also divided into groups by mode of inheritance:
  - Autosomal Dominant
  - Autosomal Recessive
  - X-Linked Disorder
  - Multifactorial Disorder
  - Mitochondrial Disorder
Etiology of Deafness

FIG. 93-1. Etiology of deafness, total population.
Autosomal Dominant Disorders

- Variation in expressivity leads to different phenotype characteristics being present in various affected members of same family
- Decreased penetrance causes obligate carrier to not have detectable phenotypic expression
- Family history may be negative with new mutation causing the disorder
Waardenburg Syndrome

- Accounts for 3% of childhood hearing impairment
- Most common form of inheritable congenital deafness
- 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
Waardenburg Syndrome

**FIG. 89-18.** Waardenburg syndrome. This mother and daughter have Waardenburg syndrome type I. Both have hearing loss and dystopia canthorum. The child also has heterochromia irides.
Waardenburg Syndrome

- Three different types that are clinically distinguishable
- Type 1 - congenital SNHL, heterochromia irides, white forelock, patchy hypopigmentation, dystopia canthorum
- Type 2 - differentiated by absence of dystopia canthorum
- Type 3 - microcephaly, skeletal abnormalities, mental retardation, in addition to features in type 1
- SNHL seen in 20% of type 1 and 50% of type 2
- Types 1 and 3 caused by mutation of PAX3 gene on chromosome 2q; Type 2 20% caused by mutation of MITF gene on chromosome 3q
- Also linked to other genes - EDN3, EDNRB, and SOX10
Stickler Syndrome

- Characterized by cleft palate, micrognathia, severe myopia, retinal detachments, cataracts, and marfinoid habitus
- Severe HL in 15%; less severe HL in 80%
- Ossicular malformations and ETD cause CHL
- Most cases attributed to mutations in *COL2A1* gene on chromosome 12
- Changes in *COLIA2* gene on chromosome 6 has also been found to cause the syndrome
Branchio-oto-renal Syndrome

- Estimated to occur in 2% of children with congenital hearing loss
- Involves ear pits/tags or cervical fistula and renal involvement ranging from agenesis and renal failure to minor dysplasia
- 75% of affected patients have significant hearing loss
- Gene felt to be responsible is located on chromosome 8q in humans and is the drosophila gene *EYA1*
Branchio-oto-renal Syndrome

FIG. 89-11. Bronchiootorenal syndrome. This 3-year-old boy has visible cup-ear deformities. He also has branchial cleft fistulae and only one kidney.
Treacher Collins Syndrome

- Includes facial malformations such as malar hypoplasia, downward slanting palpebral fissures, coloboma of lower eyelids, hypoplastic mandible, malformations of external ear or ear canal, dental malocclusion, and cleft palate
- Facial features are bilateral and symmetrical
- Ossicular malformations are common
- Transmitted AD with high penetrance, but a new mutation can be present in as many as 60% of cases
- Gene is TCOF1 on chromosome 5q which codes for the treacle protein, which is operative in early craniofacial development
Treacher Collins Syndrome
Neurofibromatosis

- Classified into two types
- Type 1 is more common with an incidence of 1:3000 persons
- Type 1 generally includes multiple café-au-lait spots, cutaneous neurofibromas, plexiform neuromas, pseudoarthrosis, Lisch nodules of the iris, and optic gliomas; acoustic neuromas occur in 5% of type 1 patients
- Type 1 caused by \( NF1 \) gene (nerve growth factor) localized to chromosome 17q
- Type 2 includes bilateral acoustic neuromas in 95% of patients, café-au-lait spots, and subcapsular cataracts
- Type 2 caused by deletions in \( NF2 \) gene (tumor suppressor) on chromosome 22q
- Both types are inherited as AD with high penetrance, also high mutation rate
Otosclerosis

- Caused by proliferation of spongy type tissue on the otic capsule
- Appears to be transmitted AD with decreased penetrance, so only 25% to 40% show phenotype
- Hormonal influence possible due to greater proportion of females affected
- Possible role for gene COLIA1 as well as an interaction with the measles viral genome
Osteogenesis Imperfecta

- Characterized by bone fragility, blue sclera, conductive, mixed, or sensorineural hearing loss, and hyperelasticity of joints and ligaments
- Transmitted AD with variable expressivity and incomplete penetrance
- Two genes have been identified: \textit{COLIA1} on chromosome 17q and \textit{COLIA2} on chromosome 7q
Nonsyndromic AD Hearing Loss

- Accounts for 15% of cases of nonsyndromic hearing loss
- Involve DNFA loci as well as an array of chromosomes
- Konigsmark and Gorlin identified several types of nonsyndromic AD hearing loss
- Several different genes have been localized for each type
## Nonsyndromic AD Hearing Loss

Table 32-1. Genes causing dominant nonsyndromic hereditary hearing loss

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Type of loss</th>
<th>Location</th>
<th>Gene</th>
<th>Study</th>
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<td>DFNA1</td>
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Dominant Progressive Hearing Loss

- Nonsyndromic, noncongenital SNHL with variability in age of onset and rate of progression
- Eventually progresses to severe to profound hearing loss
- More than 12 genes have been localized
- Four types have been identified and include: early onset, high frequency, midfrequency, and low frequency
- Extensive genetic heterogeneity for each type
Recessive Disorders

- Most common pattern of transmission of hereditary hearing loss, compromises 80% of cases of hereditary hearing loss
- Difficult to distinguish between a nongenetic disorder because may have only one child involved
- Most undetermined cases of childhood hearing loss probably due to AR pattern of inheritance
Usher Syndrome

- Prevalence of 3.5 per 100,000 population
- Affects 16,000 deaf and blind persons in the US
- Syndrome characterized by SNHL and retinitis pigmentosa
- Three subtypes divided based on severity of progression of the hearing loss and extent of vestibular involvement
  - Type 1 - congenital bilateral profound HL and absent vestibular function
  - Type 2 - moderate losses and normal vestibular function
  - Type 3 - progressive HL and variable vestibular function
- Linkage analysis reveals 5 genes for type 1, 2 for type 2, and 1 for type 3
- Ophthalmologic evaluation essential, subnormal ERG patterns have been observed by age 2 to 3
Pendred Syndrome

- Includes thyroid goiter and profound SNHL
- HL is progressive in about 15% of patients
- Majority of patients present with bilateral moderate to severe HL, with some residual hearing in the LF
- HL is associated with abnormal iodine metabolism resulting in euthyroid goiter, which is treated with exogenous thyroid hormone
- Perchlorate discharge test shows abnormal organification of nonorganic iodine and is needed for definitive diagnosis
- CT scan reveals that most patients have Mondini deformity or enlarged vestibular aqueduct
- A gene was localized to chromosome 7q in recessively transmitted families, mutations in PDS gene (sulfate transporter) have also been shown to cause this disorder
Jervell and Lange-Neilsen Syndrome

- Rare syndrome that consists of profound SNHL and syncopal episodes resulting from cardiac conduction defect
- ECG reveals large t waves and prolonged QT interval
- Cardiac component treated with beta-adrenergic blockers
- ECG should be done on all children with uncertain etiology of hearing loss
- Genetic studies attribute one form of the disorder to \textit{KVLQT1} (potassium channel) gene on chromosome 11p; gene \textit{KCNE1} has also been shown to be responsible for the disorder
Recessive Nonsyndromic Hearing Loss

- Three basic subtypes that include: congenital severe to profound, congenital moderate, and early onset.
- Congenital severe to profound type is most common
- Genetic linkage analysis has revealed at least 15 gene loci for recessive nonsyndromic hearing loss
- *DFNB2* on chromosome 13q may be most common and codes for connexin 23
- *DFNB1* on chromosome 13 codes for a connexin 26 gap gene protein which is essential for audition and auditory transport
# Recessive Nonsyndromic Hearing Loss

Table 32-2. Genes causing recessive nonsyndromic hereditary hearing loss

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Type of loss</th>
<th>Location</th>
<th>Gene</th>
<th>Study</th>
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Sex-Linked Disorders

- X-linked inheritance is rare
- Accounts for only 1% to 2% of cases of hereditary hearing loss
- May constitute about 6% of nonsyndromic profound losses in males
Norrie Syndrome

- Includes congenital or rapidly progressive blindness, development of pseudoglioma, opacification, and ocular degeneration resulting in microphthalmia
- One third of affected patients will have onset of progressive SNHL in second or third decade
- Gene has been localized to chromosome Xp; affected families have been shown to have various deletions in this region
Otopalatodigital Syndrome

- Includes hypertelorism, craniofacial deformity involving supraorbital area, flat midface, small nose, and cleft palate
- Patients are short stature with broad fingers and toes that vary in length
- CHL seen due to ossicular malformations
- Gene found on chromosome Xq
Wildervaank Syndrome

- Composed of Klippel-Feil sign involving fused cervical vertebrae, SNHL or mixed hearing impairment, and cranial nerve 6 paralysis causing retraction of the eye on lateral gaze
- Most commonly seen in the female because of high mortality in affected males
- Hearing impairment related to bony malformations of the inner ear
Alport Syndrome

- Involves hearing impairment associated with varying degrees of renal involvement
- HL may not become evident until the second decade of life
- Renal disease usually asymptomatic until causes renal insufficiency
- Defects in collagen type IV genes $COL4A5$, $COL4A3$, and $COL4A4$ have been found to cause the disorder
Nonsyndromic X-Linked Hearing Loss

- At least 6 loci on the X chromosome are known for nonsyndromic hearing loss
- Two types have been described: early onset rapidly progressive type and moderate slowly progressive type
- X-linked stapes fixation with perilymphatic gusher has been localized to DNF3 locus which encodes for POU3F4
- X-linked congenital SNHL has been mapped to Xq
- X-linked dominant SNHL has been mapped to Xp
# Nonsyndromic X-Linked Hearing Loss

Table 32-3. Genes causing X-linked nonsyndromic hereditary hearing loss

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Type of loss</th>
<th>Location</th>
<th>Gene</th>
<th>Study</th>
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<tbody>
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<td>DFN1</td>
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Multifactorial Genetic Disorders

- Some disorders appear to result from a combination of genetic factors interacting with environmental influences
- Includes clefting syndromes and the microtia/hemifacial microsomia/Goldenhar spectrum
- Goldenhar has also been shown to be transmitted AD, but this could be due to clustering
- Other conditions include increased susceptibility to hearing loss and hyperlipidemia
Mitochondrial Disorders

- Mutation in the mitochondrial genome can affect energy production through ATP synthesis and oxidative phosphorylation
- Typically involves progressive neuromuscular degeneration with ataxia, ophthalmoplegia, and progressive HL
- Nearly all mitochondria come from the mothers' egg and she transmits them to all offspring
- Other mutations have been found to produce increased sensitivity to ototoxic effects of aminoglycosides
Evaluation and Genetic Counseling

- Should be tailored to provide information to the parents about their child's hearing loss etiology and about expected pattern of inheritance of any genetic disorder
- Diligent search for etiology should be undertaken
- Obtain a detailed family history; a positive history includes family members who were under age 30 when they developed hearing impairment
- Ask about any history of hereditary traits that could be related to syndromes which includes: white forelock, premature graying, different color eyes, kidney abnormalities, night blindness, severe farsightedness, childhood cardiac arrhythmias or sudden cardiac death
Evaluation

- Previous audiologic data that had been acquired from family members should be reviewed
- Review prenatal, perinatal, and postnatal medical history
- Physical examination should look for features that are variant from normal or are dysmorphic
- Face- look for asymmetry of facial bones, skin tags, head shape, and presence of unusual hair
- Eyes- look for slanting, iris color, vision limitations, intercanthal distance, cataract, and retinal findings
Evaluation

- Ears- look for asymmetry of pinnae, malposition of the pinnae, presence of preauricular skin tags or pits, and for external auditory canal size, shape, and tortuosity
- Inspect neck for thyromegaly or branchial anomalies
- Skin- look for areas of hypo or hyperpigmentation and café-au-lait spots
- Extremities should be checked for aberrant digit size, shape, or number, and syndactyly
- Vestibular system should be examined with gait and balance
Evaluation

- Audiological evaluation should be undertaken in all suspected cases of hearing loss
- Electrophysiologic tests such as ABR, stapedial reflex, and otoacoustic emissions can be done in younger children and infants
- Audiogram that is U-shaped or cookie bite should alert you to possible hereditary hearing loss
- Get urinalysis looking for proteinuria and hematuria
- TFT's, ECG, ERG, and perchlorate discharge test as indicated by suspected syndrome
- CT for cochlear abnormalities, MRI for neuromas
Evaluation

Figure 1. Evaluation for childhood hearing impairment. *A genetics evaluation is warranted. Refer to a clinical geneticist or genetic counselor. Consider participation in research screening for deafness genes, i.e., connexin-26 gene and other genes.
Genetic Consultation

- Specific etiology still may remain uncertain even after extensive evaluation
- Consultation with clinical geneticist is recommended when hereditary hearing loss is suspected
- Genetic evaluation should consider prognosis and recurrence risk
Recurrence Risk

- AD: can range from 50% to less depending on the gene's penetrance
- AR: children of heterozygotes have 25% chance of having the disorder and 50% chance of being a carrier
  - Recurrence risk for carriers depends on the status of their mate
- X-linked: male offspring of maternal carrier of recessive trait are at 50% risk of being affected; female offspring are at 50% risk of being a carrier
- Mitochondrial disorder: depends on whether mother is homoplasmic or heteroplasmic
Recurrence Risk

- Empiric risk factor tables have been developed.
- Future offspring for a family with an only child who has an unexplained hearing loss is 10% to 16% recurrence risk.
- Each additional normal hearing child born to this family decreases the risk where as each hearing impaired child increases the risk.

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<td>All normal children</td>
<td>0</td>
<td>0.067</td>
</tr>
<tr>
<td>At least 1 deaf child</td>
<td>&gt;0</td>
<td>NA</td>
</tr>
<tr>
<td>Deaf by deaf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All normal children</td>
<td>0</td>
<td>0.097</td>
</tr>
<tr>
<td>All deaf children</td>
<td>S</td>
<td>0.097</td>
</tr>
<tr>
<td>Deaf and normal children</td>
<td>&gt;0, &lt;S</td>
<td>NA</td>
</tr>
</tbody>
</table>

\[ ^{a}x = 0.203, p = 0.25. \]
\[ ^{b}x = 0.605, p = 0.25. \]
\[ ^{c}x = 0.835, p = 0.408. \]
\[ ^{d}x = 0.789, y = 0.042, \hat{p} = 0.325. \]

NA, not applicable.
Conclusion

- Precise diagnosis is essential and diligent search for etiology should be undertaken
- Geneticist should review the clinical and laboratory data to look for a pattern to identify a syndrome or to predict the clinical course of the disease
- Accurate diagnosis enhances the accuracy of recurrence risk estimates
Conclusion

1994 Position Statement of when to perform hearing screening if universal screening is not available

I. Neonates through 28 days
   - family hx of hereditary childhood SNHL
   - in utero infection c TORCH
   - craniofacial anomalies
   - birthweight < 1500 grams
   - hyperbilirubinemia
   - ototoxic meds
   - bacterial meningitis
   - Apgars 0 to 4 at 1 minute or 0 to 6 at 5 minutes
   - on ventilator > 5 days

II. Infants 29 days - 2 years
    - parent concern, developmental delay
    - bacterial meningitis
    - head trauma assoc c LOC or skull fracture
    - ototoxic meds
    - recurrent or persistent otitis media c effusion for at least 3 months

III. Indicators for delayed onset SNHL
    - family history hereditary childhood hearing loss
    - in utero infection c CMV, rubella, syphilis, herpes or toxoplasmosis
    - neurodegenerative disorders
* This group requires hearing evaluation every 6 months until
TORCH titers
- CMV needs to be tested w/in first 3 weeks or may actually be post-natal exposure
- Persistent elevation of viral titers is suggestive of an intrauterine infection
- A deaf child that fails to develop AB to Rubella after vaccination; the etiology may be secondary to congenital rubella infection

Syphilis
- Need to check FTA-abs, IgG

Urinalysis
- Looking for protein and blood in urine

Thyroid testing
- If suspect Pendred
- May need to perform perchlorate test

EKG
- Abnormal in Jervell Lange and Refsum but is low yield

Chromosomal analysis
- Identification of AD SNHL not seen in relatives
- Mother has h/o of miscarriages
- Child has multiple cong anomalies not identified as a syndrome
- Majority of hereditary SNHL is secondary to point mutations; therefore genetic analysis not that beneficial

X:Rays
- CT
- 80% of neonates with HL do not have a morphogenetic defect
- Indicated for children ≥ 3 to look for developmental abnl of temporal bone to help explain hearing loss esp if pt is experiencing a progressive loss