Hearing Loss

1. Most common sensory deficit in human
2. 3 in ten people over age 60 have hearing loss
3. At least 1.4 million children have hearing problems
4. Estimated that 3 in 1,000 infants are born with serious to profound hearing loss
5. 6 million between 18 and 44 have hearing loss

Ear

1. Otic vesicle in embryo, eventually becomes the ear.
2. Whole structure of the ear is developed by 22 weeks of gestation (check)
3. By 18 weeks into development, embryo can sense sound. Mostly heartbeat and blood swish. By 25 weeks of development, can hear voices from outside. By week 27 can recognize their parent's voices.

Structure

1. Outer ear
    a. collects sound waves
    b. travel to:
2. Middle ear
    a. tympanic membrane/ear drum
    b. three tiny bones which vibrate, carry sound to:
3. Inner ear
    a. fluid filled structures move because of vibrations. Impinge on sensory cells (hair cells)
    b. When hair cells get excited, change into chemical impulse which changes to nerve impulse to brain, perceive sound.

Inner ear

1. Divided into two structures
    a. Vestibular system
        i. canals
        ii. part that is responsible for balance
    b. Cochlea
        i. responsible for hearing
        ii. organ of corti-produces nerve impulse in response to vibration
        iii. three rows of outer hair cells
            1. will fine tune/amplify vibrations being receives
        iv. one row of inner hair cell
            1. send signal to brain via auditory nerve
        v. Tips of both types of hair cells have stereocilia
        vi. similar to cilia on kidney cells
        vii. Tectorial membrane
            1. receives vibration from middle ear

2. stereocilia make contact with membrane, feel vibration. Tiplink is deflected, allows ions to go inside cell body and chemical signal is generated.

Hearing depends on two parameters
1. Frequency
    a. measured in Hz
    b. higher the frequency, higher the tone.
    c. Lower pitch is lower sound.
2. Intensity
    a. measured in dB
    b. how loud it sounds

1. Conversatioal speech
    a. 45-60 db
2. Hearing Loss
    a. Mild: 20-40 db
    b. Moderate: 40-60 db
    c. severe: 60-80 db
    d. Profound: more than 80 db

Forms of hearing loss
1. Conductive hearing loss/deafness
    a. any damage to external or middle ear
    b. can be something like too much ear wax, middle ear infection
2. Sensorineural hearing loss
    a. any abnormality between hair cells and the brain
    b. could be genetic, head injury, high blood pressure, etc.
3. Mixed
    a. when both conductive and sensorineural hearing loss
4. Presbycusis
    a. age related hearing loss
    b. changes in the inner ear
5. Tinnitus
    a. ringing in the ears
    b. usually don't know the reason

Other features
1. Syndromic: other organ systems involved
2. nonsyndromic: deafness only
3. Time of onset
    a. congentical: present at brith
    b. Early onset or Late onset

Hearing loss causes
1. environmental
    a. acoustic trauma

b. ototoxicity
c. infection
2. Genetic
a. 75% autosomal recessive disorder
b. 10-15% autosomal dominant disorder
c. x-linked
d. mitochondrial
e. chromosomal

Nonsyndromic Hearing Loss
1. DFNA=autosomal dominant
2. DFNB=autosomal recessive
3. DFN=x-linked
4. Congenital/prelingual
a. deaf before developing language skills
b. autosomal recessive
5. postlingual
a. deaf after developing language skills
b. autosomal dominant or mitochondrial

1. Mutations in Connexin 26 (GJB2)
a. major contributor in
i. nonsyndromic deafness (50% of all recessive deafness cases)
ii. sporadic cases (10%)
b. DFNB1
c. Protein
i. transmembrane protein
ii. single connexIn forms multimer (6) called connexOn which forms an intercellular channel. gap junction protein.
iii. Gap junctions are a way to recycle potassium in fluid in the inner ear.
iv. channels are found in supporting cells and in spiral limbus area
v. Mutations in this gene have two hotspos
1. 35delG
a. 70% of mutations will be this: deletion of G at 35
b. 1/40
2. 167delT
a. Ashkenazi 1/25 have this

1. Waardenburg syndrome (WS)
a. First described by a dutch dotor who noticed people with two different colored eyes
b. Affects 1/100,000 individuals
c. Autosomal dominant
d. 3 primary defects
i. hearing
ii. pigmentatin

iii. facial structure
e. Iris heterochromia
i. different colored eyes. Usually one blue and one brown
ii. Wider spaced eye
f. Partial albinism
g. by 12, some gray or white hair
h. congenital deafness
i. Locus Hetereogenetity
i. mutations in different geens can cause similar phenotype
ii. PAX3, MITF, SOX10, EDN3, EDNRB and more
iii. most are transcription factors

1. Pendred Syndrome
a. Autosmoal recessive
b. accounts for 1-10% of hereditary deafness
c. endocrine dysfunction and hearing loss
d. congential hearing loss
i. sometimes doesn't develop until later in early children
e. problems with balance
f. enlargement of thyroid
i. called goiter
ii. still functional, however
g. Gene: SLC26A4
h. protein: pendrin
i. permeable anion exchanger
j. Transport negatively charged ions (Iodide, biocarbonate, etc)
k. pH of fluid in inner ear is very important.
l. At different compartments, different pH.
m. Pendrin transports biocarbonate in and out to maintain pH homeostasis

1. Usher Syndrome
a. Deafness, blindness, vesibular symptoms
b. Three types based on
i. symptoms
ii. onset
iii. severity
c. 3-5% of all cases of childhood deafness
d. Type I
i. Most severe form
ii. profound hearing loss
iii. Reinitis pigmentosa (RP), typically night blindness at ten to complete blindness
iv. balance problems. Delays development in walking, sitting up
e. Type II
i. little less severe
ii. moderate to severe hearing loss
iii. RP. Visual problems begin as teenagers, progress to complete blindness

iv. normal balance

f. Type III
   i. least severe
   ii. progressive hearing loss. Highly variable when hearing is lost. Usually at adulthood
   iii. RP: progressive, usually blind by mid adulthood
   iv. some balance problems that worsen with age. Doesn't occur until adulthood

g. Animal models
   i. Waltzer-completely deaf, retinal degeneration, vestibular problems
   ii. Normal mouse has three rows of outer hair cells. The stereocilia are completely disorganized in waltzer.

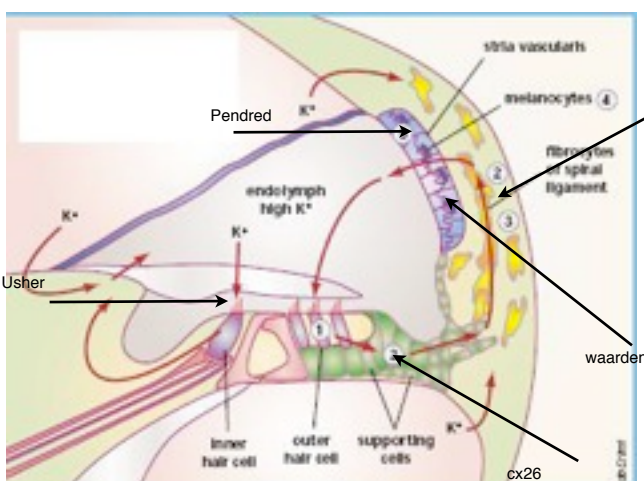
h. UsherD: Catherin 23 important for links in organizing stereocilia, if gone, the tiplinks don't work, can't polarize cell.

i. Usher1B: MYo7a motor protein, important for tiplink tension. When disrupt, get deafness.

j. Usher 1C: Harmonin. BInds to my07a and binds to actin filaments that make up stereocilia.

k. all important for stereocilia. any one is defective, get Usher

1. Allelic heterogeneity
   a. Phenotype depends on nature of mutation within the gene
   b. C to T substituion in Exon 1, USH1b. 9bp deletion in exon 22=DFNA1. T insertion exon 28=DFNB2. All within the same gene.



Mitochondrial inheritence
1. From mom

1. Aminoglycoside-induced deafness
   a. one of the most common types of acquired deafness
   b. High doses of aminoglycosie will be toxic to ear.
   c. Some will have no tolerance, will get deafness with even a little bit.
   d. Carry mutation in the MTRN1 gene which codes for 12S rRNA. (A to G)
   e. Exposure to aminoglycoside causes irreversible hearing loSs
   f. About 40% of individual with A1555G not treated with drug will develop hearing loss by age 30.
   g. about 80% will develop hearing loss by age 65
   h. Prevalence in US population is 1%.

1. Nuclear and mitochondrial genes affect age related hearing loss
   a. study showed that two different types of mice which are genetically identical and homozygous for A genes on everything it has. Other is homozygous for c genes on everything it has.
   b. Series of crosses
   c. tested their hearing. The higher the number, the worse the hearing
   d. Next step, same crosses but switched male and female.
   e. A mice have mutation in MtGene tRNA which codes for arginine

1. Aims of diagnosis
   a. prevent further hearing loss
   b. Predict associated clinical manifestations
   c. provide genetic counseling

1. Need to address
   a. Acquired or inherited
   b. syndrome or nonsyndromic
   c. mode of inheritance if genetic
   d. conductive or sensorineural
   e. vestibular involvement

1. Cultural differences in Deaf population

Functional auditory hair cells produced in the mammalian cochlea by *in utero* gene transfer

1. Background
   a. hair cells in mammalian inner ear do not regenerate
   b. hair cells are terminally differentiated
   c. In mice, hair cells are “born” between E13 and E15.

d. Would the technique in this paper work for waltzer mice? No because the defect is in the stereocilia themsleves. They don't have a lack of hair cells.
e.