Non-Syndromic Deafness

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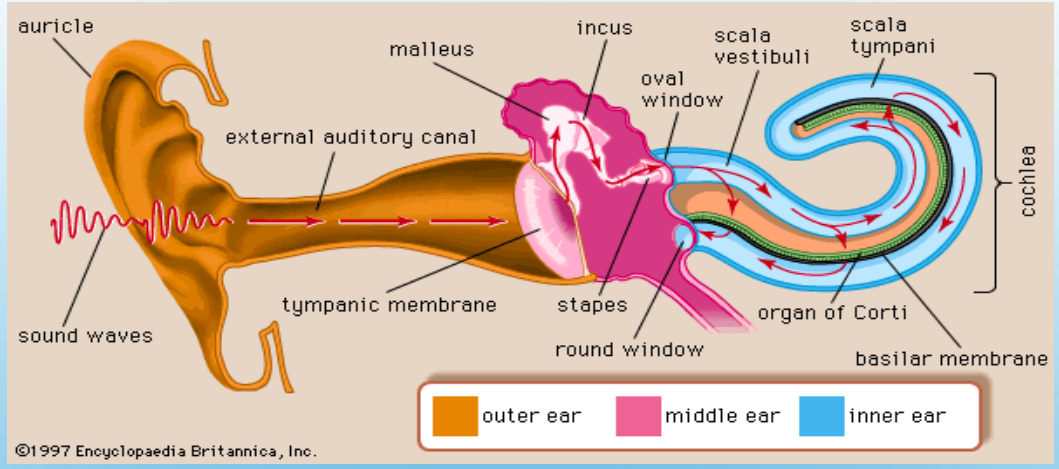
Physiology

- Three to four children out of one thousand are born in the USA with a hearing loss.
- Hearing loss is measured from mild, moderate, moderately severe, severe, and profound with unilateral and bilateral for one or two ears that are affected.
- Non-syndromic deafness means there are no symptoms other than the hearing loss.
- The hearing loss is present at birth and is often severe or profound with some cases having a lesser degree of hearing loss.
- The ear has three parts, inner, middle, and outer. Hearing loss that occur in the outer or middle ear are called conductive hearing loss, while in the inner ear it is called sensorineural hearing loss (nerve deafness).
- The focus is on sensorineural hearing loss due to malformed hair cells in the cochlea.
- While there are no symptoms other than the hearing loss, cognitive impairment can occur if the affected individual goes undiagnosed up to five or six years old when they are too old to begin learning how to speak their language. This also includes difficulty in learning sign language.


auricle
malleus
incus
scala vestibuli
scala tympani
oval window
external auditory canal
cochlea
sound waves
tympanic membrane
stapes
round window
organ of Corti
basilar membrane
outer ear
middle ear
inner ear
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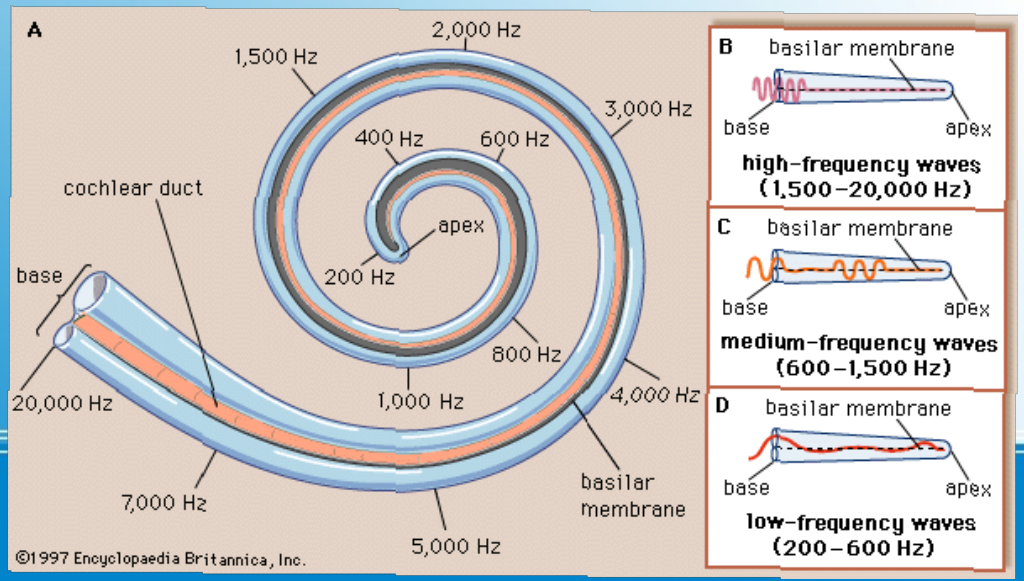
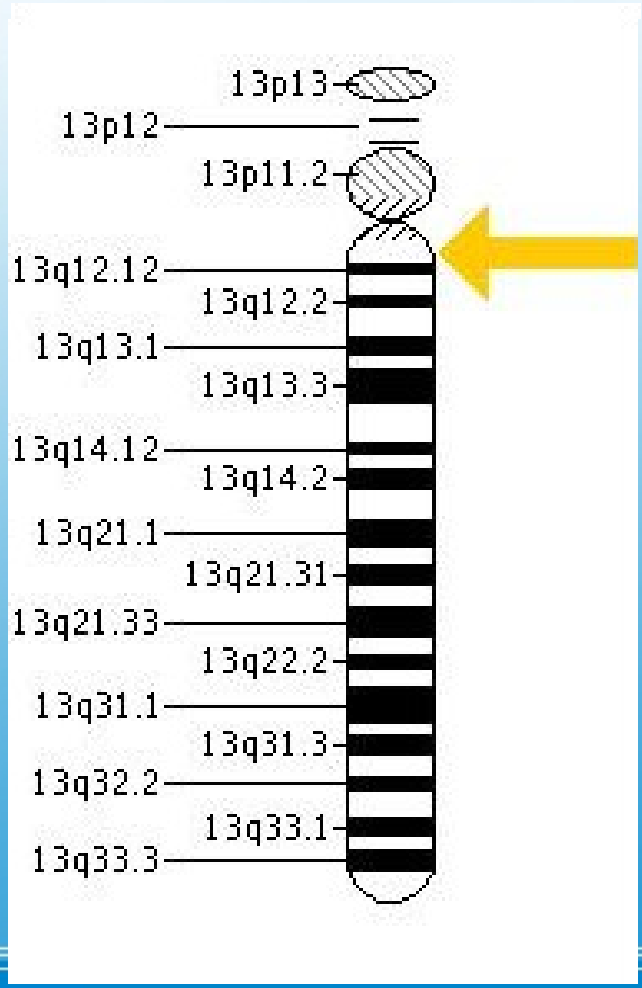
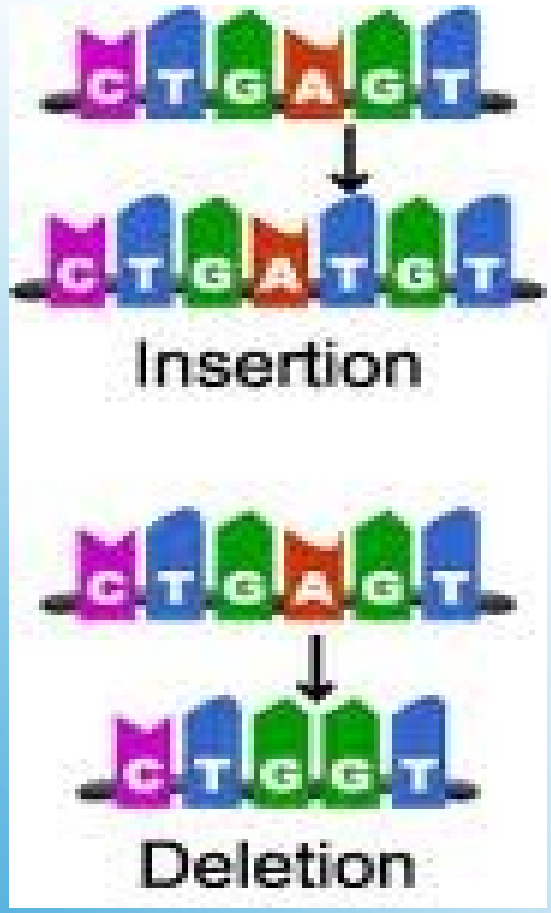

A
2,000 Hz
1,500 Hz
3,000 Hz
400 Hz
600 Hz
cochlear duct
apex
200 Hz
base
800 Hz
20,000 Hz
1,000 Hz
4,000 Hz
7,000 Hz
basilar membrane
5,000 Hz
©1997 Encyclopaedia Britannica, Inc.
B
basilar membrane
base
apex
high-frequency waves
(1,500–20,000 Hz)
C
basilar membrane
base
apex
medium-frequency waves
(600–1,500 Hz)
D
basilar membrane
base
apex
low-frequency waves
(200–600 Hz)

Molecular Causes

- Transmission patterns of the mutations, from most common to least, are autosomal recessive (~75 to 80%), autosomal dominant (~20 to 25%), X-linked (~1 to 2%), and mitochondrial (less than 1%).
- There are over 70 different genes that can cause hearing loss such as the MT-RNR1, ATP2B2, MYO1A, and GJB3 genes. There are over 90 specific mutations on the GJB2 gene alone that can cause the disorder. The most common mutation is named 35delG.
- The 35delG mutation on the GBJ2 gene is responsible for 80% of autosomal recessive deafness.
- 35delG is a guanine-base deletion and is a mutation located on the short arm of chromosome 13 called 13q11-q12.
- It terminates an RNA sequence by changing a Valine codon into a stop codon and creating a deformed version of the protein connexin 26 and the hair cells in the cochlea can't communicate neural signals to each other and send the signals to the brain to be interpreted as sounds.


13p13
13p12
13p11.2
13q12.12
13q12.2
13q13.1
13q13.3
13q14.12
13q14.2
13q21.1
13q21.31
13q21.33
13q22.2
13q31.1
13q31.3
13q32.2
13q33.1
13q33.3


C T G A G T
C T G A T G T
Insertion
C T G A G T
C T G G T
Deletion

Current Treatments

- Hearing aids are used for people with mild to moderately severe hearing loss and they work by amplifying sounds, since the damaged hair cells can still transmit loud sounds.
- Cochlear implants benefit those with severe to profound deafness and involve invasive surgery.
- The cochlear implants completely bypass the damaged ear by sending sounds waves to the implant which is connected to the auditory nerve, and the nerve sends the sounds to the brain.
- This is achieved by a process called transduction where stimuli are converted from one form into another. Sound is converted from air waves into electrical signals and then into neural impulses.
- It may be best to first spend some time using hearing aids and then decide to get cochlea implants, since the surgery is permanent.
- Most current efforts on treatments are focused on improving the quality of hearing that hearing aids and cochlear implants can give and increasing the number of infants screened for deafness. Currently, 95% of infants are tested for deafness.

Proposal Cure and Limits

- Gene therapy uses viral vectors to insert new DNA into cells to replace the defective sequences.
- It's main advantage is that there are a large variety of vectors that can be used for insertion and one can use different vectors for specific cases or different genetic mutations.
- Trial testing on guinea pigs and mice has revealed the development of new hair cells in the cochlea several weeks after injection.
- Current obstacles involve detecting deafness even earlier, possibly before birth, to be able to alter the hair cells before the effective hair cells form, and there needs to be more testing to improve the viral vectors to ensure better development, since the hair cells don’t always form perfectly.
- There are problems such as the immune system rejecting the vector. However, the inner ear is a place where the immune system is less sensitive and the risk of rejection is lower than in the rest of the body.
- Studies have shown adeno-associated virus (AAV), AV virus, and lentivirus (LV) as the best viral vectors to use. AAV is the most compatible with the RNA sequences in the cochlea. AV is better for altering DNA and LV has not been in clinical testing yet.
- The final problem with gene therapy is the delivery route. Insertion through the scala tympani is best since it is part of the cochlea and close to the hair cells, allowing the vectors to diffuse through the cochlea. However, AAV cannot yet diffuse through the barrier.

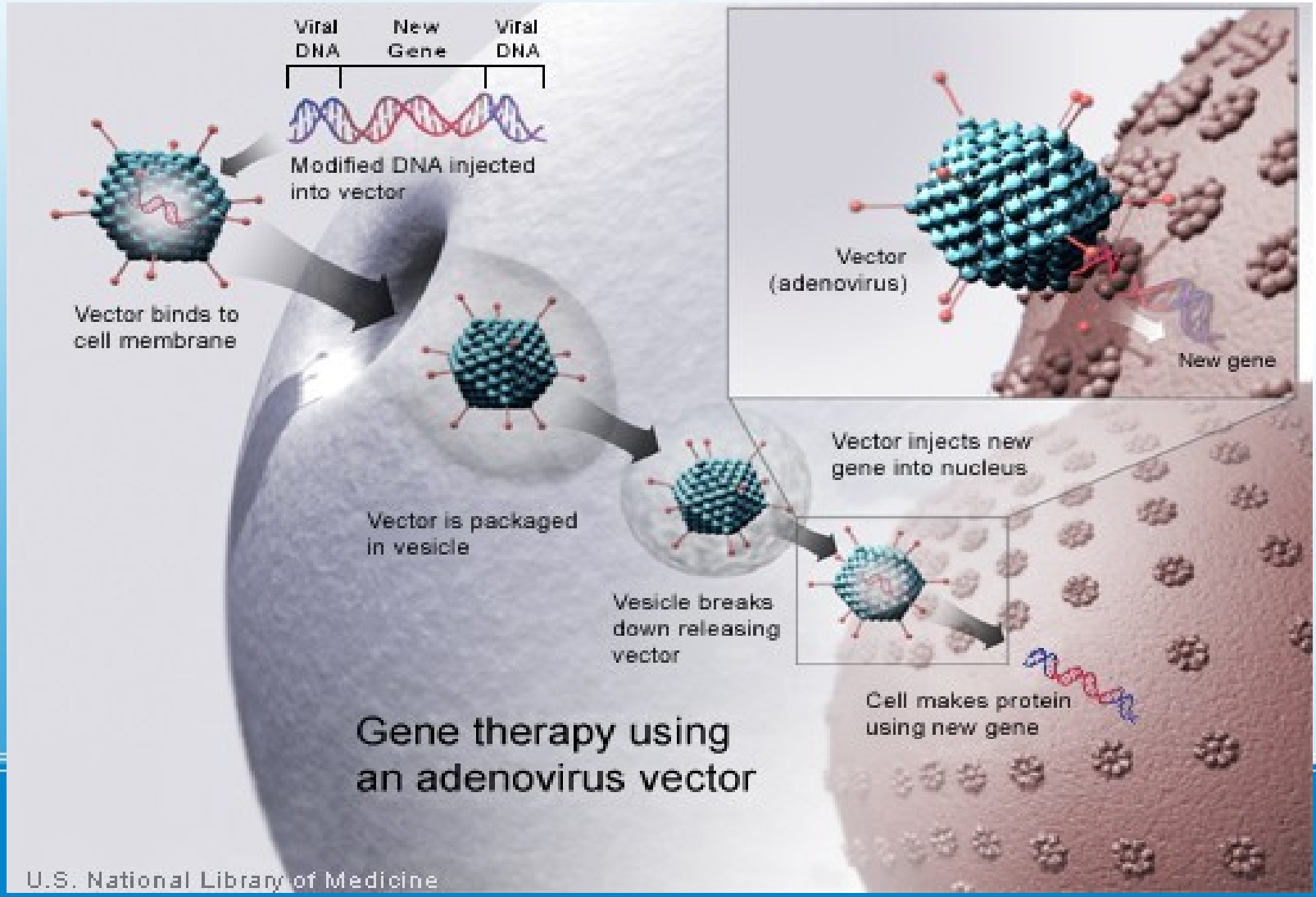

Viral DNA
New Gene
Viral DNA
Modified DNA injected into vector
Vector binds to cell membrane
Vector (adenovirus)
New gene
Vector injects new gene into nucleus
Vector is packaged in vesicle
Vesicle breaks down releasing vector
Cell makes protein using new gene
Gene therapy using an adenovirus vector
U.S. National Library of Medicine

Image References

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