

Hearing and Genetics

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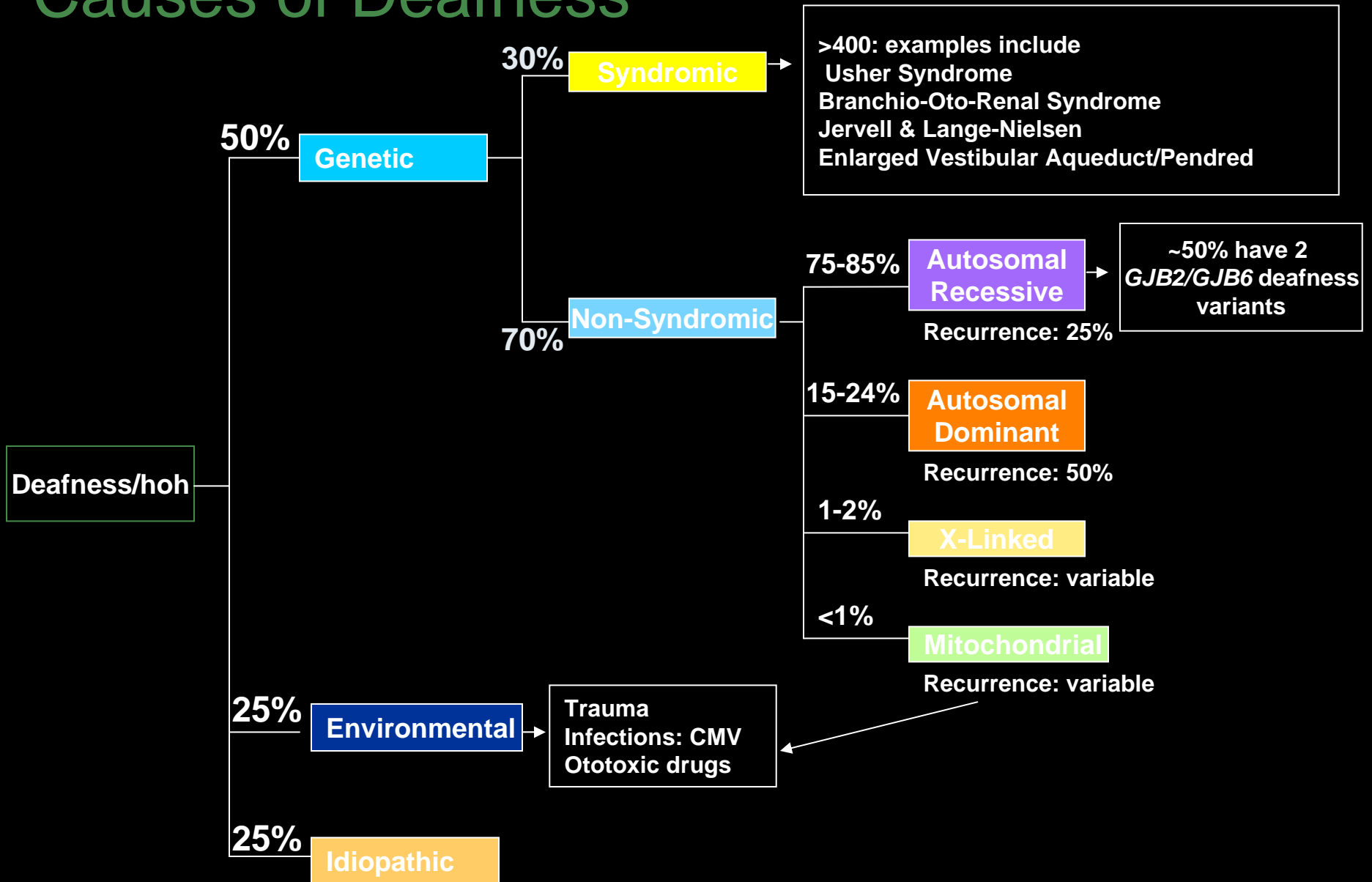
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Institute of Human Genetics

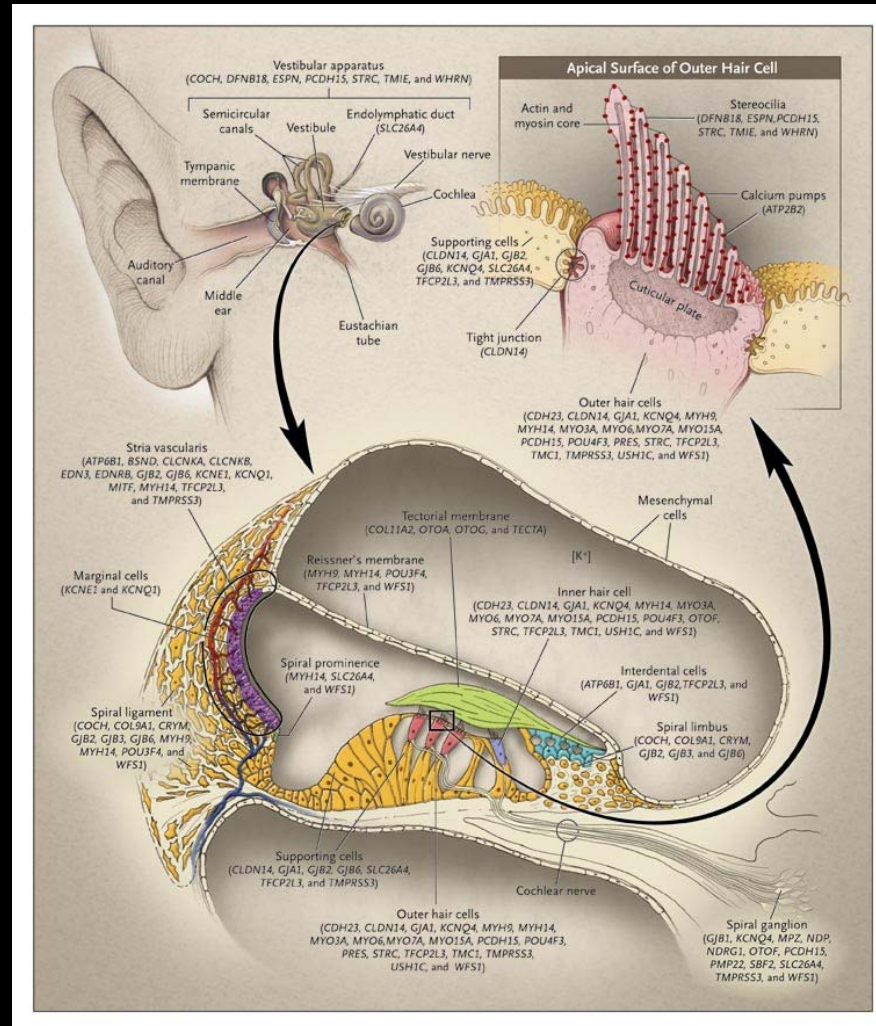
Talk Objectives

- A genetic basis of deafness/hoh can be identified in half of all individuals.
- Understanding the genetic basis of deafness informs medical management.

Causes of Deafness



View of the Outer, Middle, and Inner Ear with a Cross-Sectional View of the Cochlear Duct and a View of Hair Cells



Morton C and Nance W. N Engl J Med 2006;354:2151-2164



The NEW ENGLAND
JOURNAL of MEDICINE

GJB2/GJB6

- Genes that encode the proteins Connexin 26 and Connexin 30
- Genetic variants in *GJB2/GJB6* are the most common cause of deafness worldwide
- Associated with up to half of all non-syndromic deafness



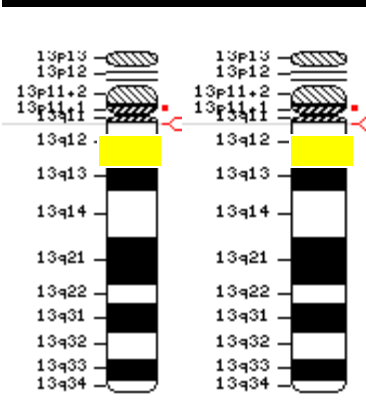
Connexin related deafness is common

- Green et al. JAMA, 1999
 - Midwestern US population
 - 52 individuals with deafness
 - 42% had two significant variants in *GJB2*
 - 29/41 variants were 35delG



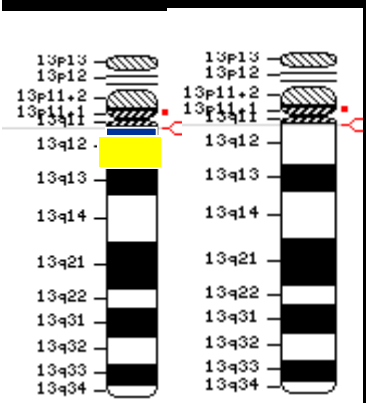
Connexin 26 related deafness

- Recessive: both genes have a variant



2 changes in *GJB2*

Cx 26 deafness



1 change in *GJB2*

usually carrier

No changes in *GJB2*

Not Cx 26 related

There are nearly 100 different deafness associated variants in *GJB2*

- **Changes in *GJB2* gene result in changes in the Connexin 26 protein:**
 - truncating variants - either a small or no protein is produced
 - missense variants- a protein is produced but may not localize, interact or function normally



Carrier Frequency of *GJB2* deafness variants

- 35delG- European (2-4%)
 - just as frequent as cystic fibrosis carriers
- 167delT-Ashkenazi (4-7%)
- 235delC-Japan (1-2%)
- V37I- Taiwan (11.6%)



GJB2/GJB6 related deafness/hoh: Phenotype

- Sensorineural deafness/hoh
- Bilateral, some reports of unilateral
- Generally considered non-progressive, but evidence for progression in some cases
- Normal temporal bone morphology
- Genotype-phenotype correlations
 - Protein truncating variants == audiograms tend to fall into severe-profound range
 - Non protein truncating variants == audiograms tend to fall into mild-moderate range
- Extra-auditory findings: none
 - Non-syndromic



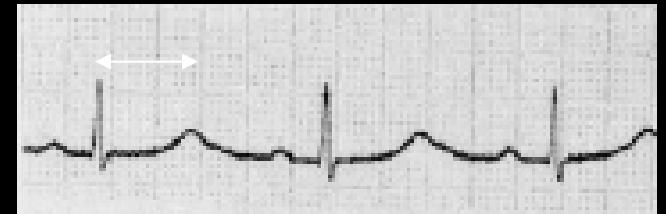
There are over 400 syndromes associated with d/hoh.



Pendred Syndrome



Usher Syndrome



Prolonged QT interval

Jervell & Lange-Nielsen syndrome

Some have very serious consequences..

Syndrome

- Syn = with
- Drome = runs
- Example: Pendred Syndrome
 - Deafness with EVA that runs with thyroid goiter



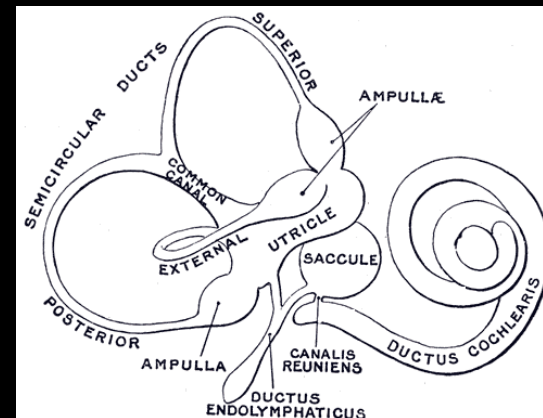
Enlarged Vestibular Aqueduct Syndrome

- Deafness that runs with EVA
- Isolated
 - Deafness is the only finding; MOST COMMON
- Can occur with other syndromes
 - Pendred Syndrome
 - Branchio-oto-renal
 - Waardenberg Syndrome
 - CHARGE
 - Other rarer syndromes



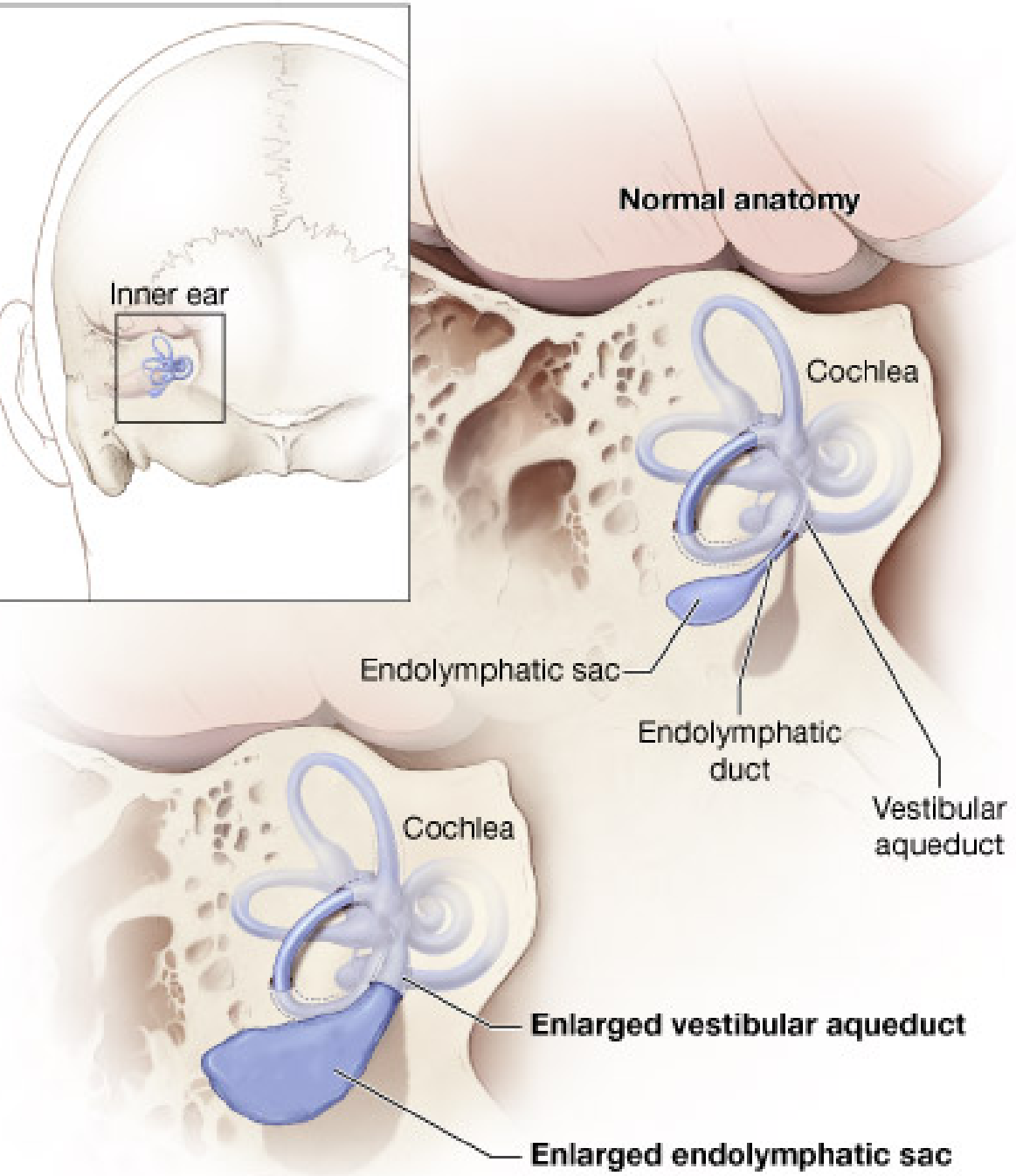
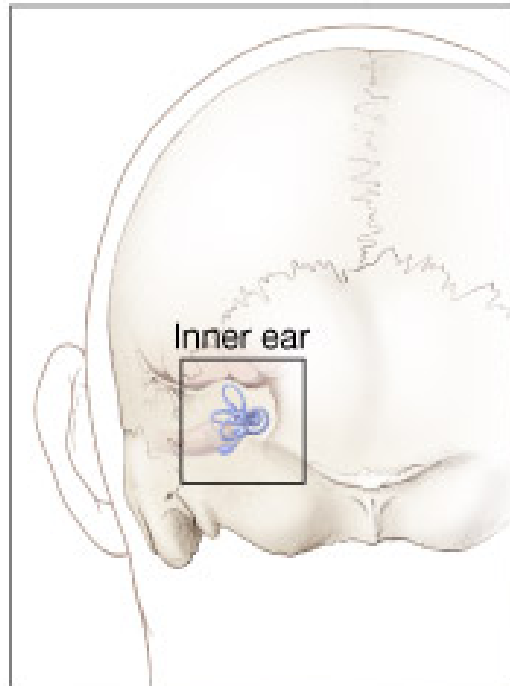
What is the vestibular aqueduct?

- Bony structure from the inner ear to the brain
- Carries the endolymphatic duct
 - Contains inner ear fluid
- Also carries blood vessels



Why does enlarged vestibular aqueduct matter?

- Most common bony inner ear malformation in children with sensorineural deafness.
- It is more common in females.
- It is commonly in both ears but can occur in only one ear.
- Can be associated with progression of deafness/hoh.



Enlarged Vestibular Aqueduct



unaffected



affected

Pendred syndrome

- Clinical features:
 - Variable sensorineural deafness
 - Progressive
 - Goiter, showing incomplete penetrance
 - Enlarged vestibular aqueduct



- Inheritance:
autosomal recessive

Photographs of mild goiter
provided by Richard JH Smith, MD.

ACMG

- Gene: SLC26A4

Branchio-oto-renal syndrome (BOR)

- Found in 7.5% of deafness at birth
- Inheritance:
autosomal dominant
- Genes:
EYA1 (8q13.3)
-other genes have been identified
but testing is not yet available



Photograph of a branchial fistula
provided by
Richard JH Smith, MD.

Branchio-oto-renal syndrome (BOR)

- clinical findings:
 - sensorineural, conductive or mixed deaf/hoh
 - branchial pits, cysts and/or fistulae
 - renal dysplasia or aplasia
 - malformed pinnae
 - ear pits and/or tags



Photograph of a malformed pinna provided by
Richard JH Smith, MD.

Waardenburg syndrome (WS)

- Prevalence: 3% of deaf children
- Inheritance: autosomal dominant; some cases may be autosomal recessive
- Many Genes:
PAX3 (most common)
MITF, SOX10, EDN3, EDNRB



Photograph of white forelock from V. Sybert "Genetic Skin Disorders."

Waardenburg syndrome (WS)

- Clinical findings:
 - profound sensorineural deafness present at birth
 - two different colored or brilliant blue eyes
 - white patch of hair
 - severe constipation/absent nerve cells in the intestines



Photographs showing heterochromia irides (top) and dystopia canthorum (bottom) provided by Richard JH Smith, MD.

Vision and Hearing

Usher syndrome

- Prevalence: 3-6% of all deaf children
- Inheritance: autosomal recessive
- Many Genes:
MYO7A, PDZ73, CDH23, PCDH15, SANS, Usherin, GPR98, WHRN, CLARIN1



Photograph shows the left fundus of an individual with Usher Syndrome Type II. Photograph provided by Richard A Lewis MD.

Usher syndrome

- Clinical findings:
 - Type I, profound congenital sensorineural deafness, absent vestibular responses, retinitis pigmentosa (RP) usually beginning in the 1st decade
 - Type II, mild to severe congenital sensorineural deafness mainly in higher frequencies, deafness can be mildly progressive, normal vestibular responses, RP usually begins in 1st or 2nd decade
 - Type III, progressive deafness, variable vestibular responses, variable age of onset of RP

Heart and Hearing

Jervell & Lange-Nielsen syndrome (JLNS)

- Prevalence: ~1% of all d/hoh children
- Inheritance: autosomal recessive
- Genes: KVLQT1
KCNE1

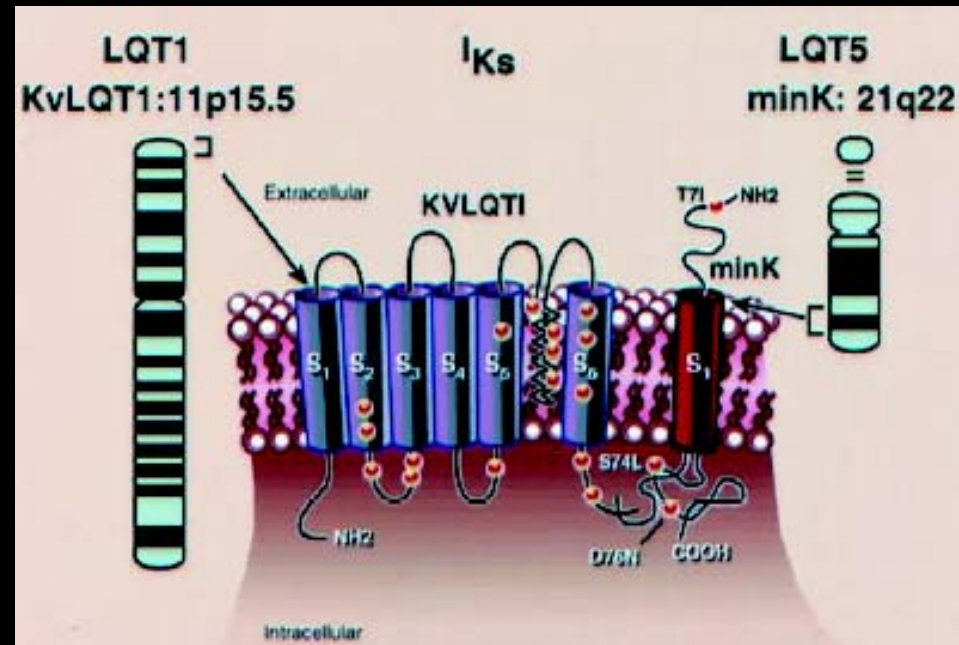
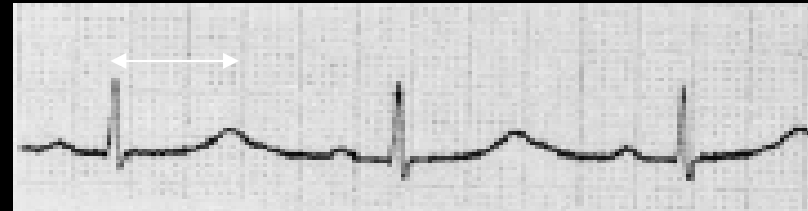


Image from Towbin and Vatta.
Am J Med 2001;110:386-398.

Jervell & Lange-Nielsen syndrome (JLNS)

- Clinical findings:
 - Severe to profound congenital sensorineural deafness
 - Prolongation of the QT interval
 - Syncope
 - Sudden death

Normal QT interval



Prolonged QT interval

Top image from the ECG library,
Dean Jenkins and Stephen Gerred
<http://www.ecglibrary.com/norm.html>.
Bottom image from Towbin and Vatta.
Am J Med 2001;110:386-398.

Case Studies

Case 1

- L is a newborn who refers on the newborn hearing screen
- Diagnostic testing at 1 month reveals bilateral moderate sensorineural deafness
- L is fitted with hearing aids
- CT scan shows normal vestibular aqueduct/temporal bone morphology
- Parents are of European origin
- No family history of hearing loss

Case 1

- Genetic testing for *GJB2/GJB6*
 - Mutation testing reveals two variants:
167delT/35delG
 - Health care implications: no other concerns for potential of vision loss or other organ systems.
 - Hearing loss is stable over 2 years

Case 2

- S is a 15 month old with fluctuating bilateral sensorineural deafness
- Failed newborn screen
- Hearing aids placed but problems with change in severity with progression over time
- Testing for *GJB2/GJB6*: no hearing loss variants
- No family history of hearing loss
- CT scan performed

Case 2

- CT showed bilateral enlargement of the vestibular aqueduct
- Genetic testing of *SLC26A4*
 - M1T/G197R
- Health Care Issues:
 - On going risk for thyroid goiter
 - Annual thyroid function testing
 - Close follow-up for progressive hearing loss

Case 3

- B is a 5 year old boy with profound SNHL
- B has no sign nor oral language
- B walked at 2 years of age

Case 3

- CT read as normal
- Genetic testing for USH1b (MYO7a)
 - Two variants 582delC/5886-5888delCTT
- Health care issues
 - Ongoing vision monitoring
 - Pt will have night blindness and progressive vision loss
 - Potential for gene therapy in the future to preserve sight

Case 4

- M is a 5 month old with profound SNHL
- Identification by newborn screening
- Hearing aids placed by 2 months but little response
- His mother reported that he responded to a very loud alarm at close range
- CI is being planning in the coming months
- CT scan normal

Case 4

- Genetic testing was negative
- Cause of deafness unknown
- Parents informed of 14% chance of future children who are d/hoh
- Ongoing medical management
 - Eye examination
 - Follow up for normal development of milestones

Talk Objectives

- A genetic basis of deafness/hoh can be identified in half of all individuals.
- Understanding the genetic basis of deafness informs medical management.

Thank you



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