Genetic Causes of Hearing Loss

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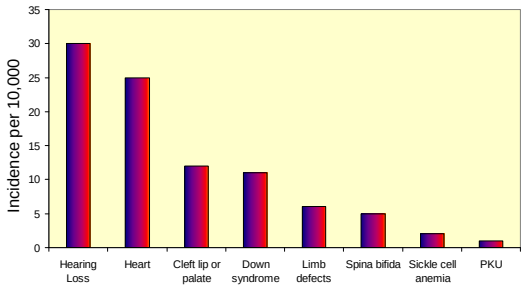
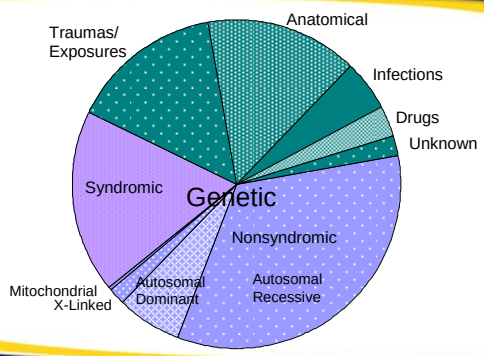
PARTNERS HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE | HARVARD MEDICAL SCHOOL

Hearing Loss is the Most Common Congenital Anomaly



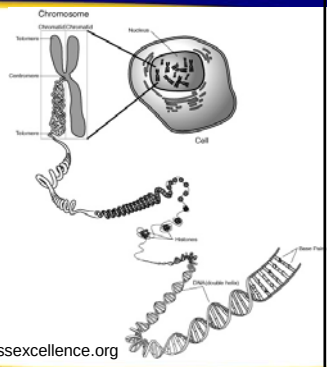
Major Causes of Hearing Loss



DNA is Highly Compacted into Chromosomes

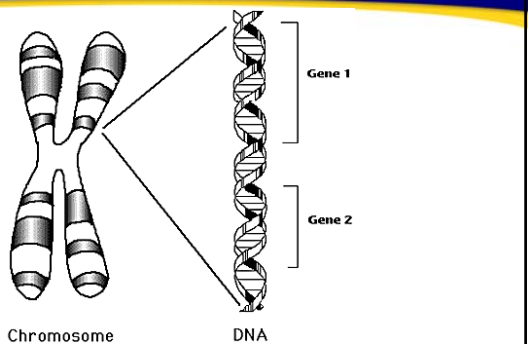
The DNA from one cell stretches 7.5 feet.

All of the DNA in your body would stretch from here to the moon 300,000 times.



http://www.accessexcellence.org

Genes are found on chromosomes



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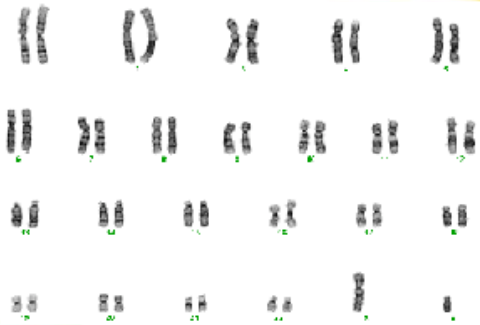
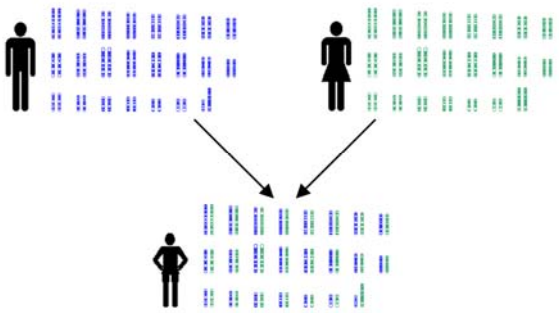
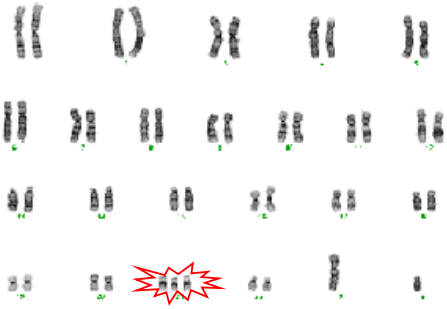
Human Karyotype



We inherit two copies of each chromosome (and each gene), one from each parent.



Chromosome Abnormalities



Trisomy 21 (Down's Syndrome)

How is hearing loss inherited?

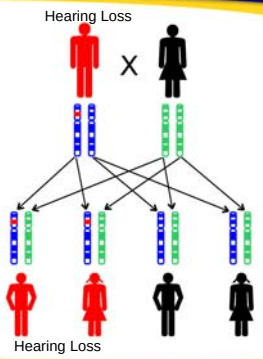
Autosomal Dominant Inheritance

Some forms of hearing loss are caused by only one copy of a mutated gene.

This hearing loss is seen in every generation.

If a parent has a dominant mutation, each child has a 50% chance of inheriting it.

Dominant hearing loss is more often seen with later-onset forms of genetic hearing loss.



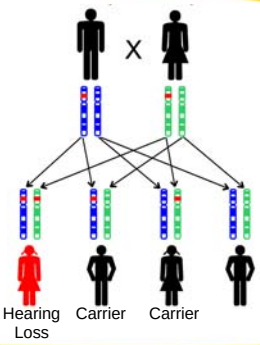
Autosomal Recessive Inheritance

The majority of childhood hearing loss is recessive, meaning both copies of a gene must have variants.

Often, there is no family history of hearing loss.

Each child will have a 25% chance of having hearing loss.

A carrier is a person who carries one copy of a recessive mutation, but does not have hearing loss.



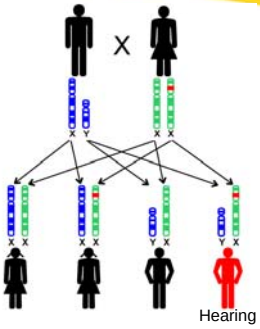
X-Linked Inheritance

Only males have hearing loss.

Each son will have a 50% chance of having hearing loss.

Each daughter has a 50% chance of being a carrier.

Example: POU3F4



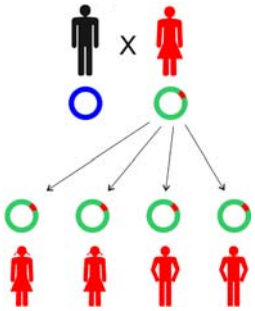
Mitochondrial Inheritance

Only the mother passes mitochondria to her children.

All children will inherit a mitochondrial variant from their mother.

Mitochondrial hearing loss is often variable in its age of onset, severity and progression.

Examples:
12S rRNA (MTRNR1)
tRNASer^{UCN} (MTTS1)



Genetic Testing

What is it?

Determine whether you have a mutation (variant) in a gene which can result in a trait such as hearing loss.

What can be tested?

Metabolic substances (e.g. PKU)
Proteins (e.g. IRT for Cystic Fibrosis)
Chromosomes (e.g. Down's Syndrome)
Genes (e.g Connexin 26)

All of these are tested using a blood sample.

How is genetic testing done?

- Physician (ENT, PCP, pediatrician, geneticist) or genetic counselor discusses testing with the patient/family and they decide to order genetic testing
- Blood sample is obtained (sometimes saliva or cheek brushes can be used) and sent to the lab by overnight mail
- Testing is completed and report written
- Lab returns report to physician
- Physician or genetic counselor communicates results to patient
- If positive, family member testing becomes available for identified variants for a fraction of full test cost

DNA Testing

DNA

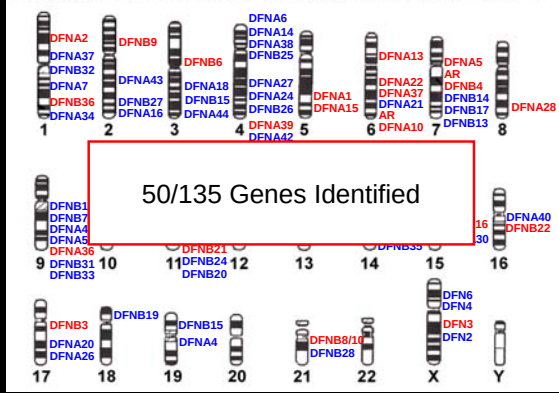
Normal DNA Sequence

ATG GTG CCT CAG GAT

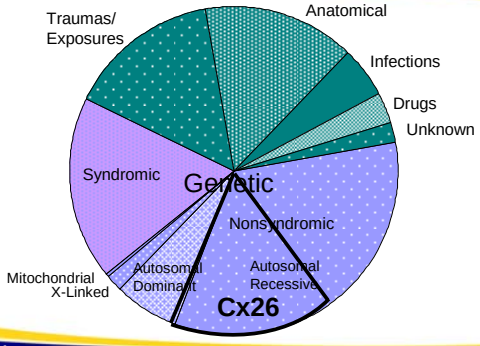
ATG GTG CCT T**A**G GAT

DNA Sequence with Variant

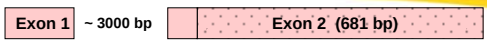
Nonsyndromic Deafness Genes in the Human Genome



Major Causes of Hearing Loss



GJB2 - Connexin 26



DFNB1 (Recessive) Mutations

Missense: M1V, T8M, G12V, K15T, S19T, I20T, R32C, M34T, V37I, A40E, A40G, G45E, E47K, W77R, V84L, L90P, V95M, H100Y, S113R, delE120, K122I, R127H, R143W, E147K, P175T, R184P, R184W, S199F, L214P, 05INS4, I203K, N206S, S139N, H100, E101G, L90V, M93I, 486INST, Q80R, I82M, S85P, A88S, L174R, L79P, Q80P, S19T, I20T, V27I+E114G, R32L, R165W

Nonsense: W24X, W44X, E47X, Q57X, Y65X, Y97X, Q124X, Y136X, W112X, W172X, C64X, Q80X, E147X

Caucasian AJ Asian

Frameshift: 31del14, 31del38, 35delG, 35insG, 51del12insA, 167delT, 176del16, 235delC, 269insT, 299delAT, 314del14, 333delAA, 290insA, 310del14, 312del14, 509del14, 509insA, 515 del17, 631delGT, 504insAAGG, 515del17, 572delt, 645delTAGA, 302del3, 469delG

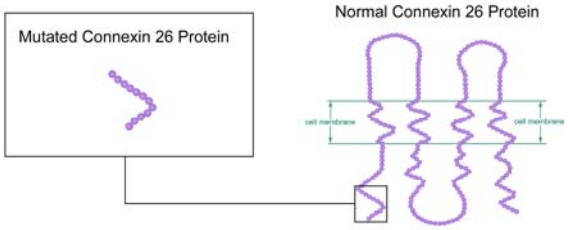
Splice Site: IVS1+1G>A

Carrier Rates and Common Mutations
Caucasian: 2-3% (35delG common)
Ashkenazi Jewish: 3-4% (167delT common)
Asian: (235delC and V37I common)
African American: (R143W may be common)

Base Deletion: Cx26 – 35delG

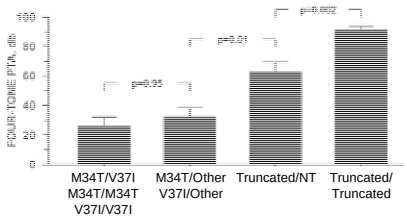
…ACGATCCTGGGGGGTGTG…normal

…ACGATCCTGGGGG TGTG…variant



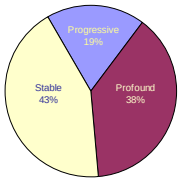
Severity of Cx26 Hearing Loss

Total = 126 patients



Kenna MA, Feldman HA, Neault MW, Frangulov A, Wu B-L, Fligor B, Rehm HL. Audiologic phenotype and progression in GJB2 (Connexin 26) hearing loss. Submitted.

Progression of Cx26 Hearing Loss



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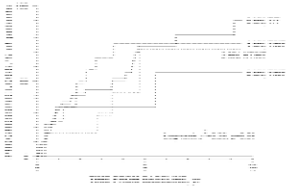

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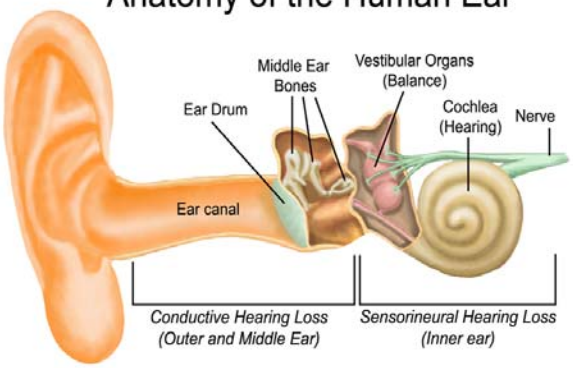
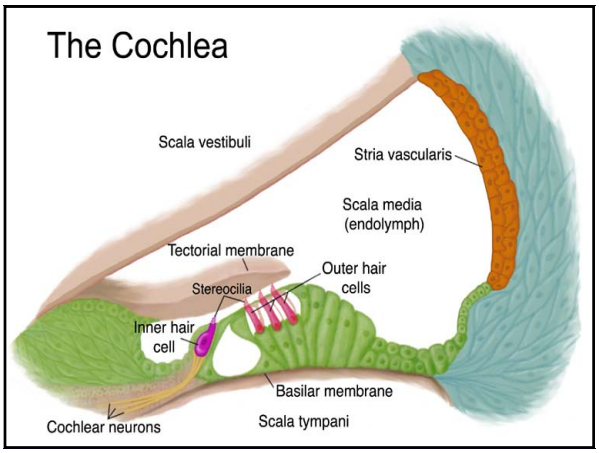
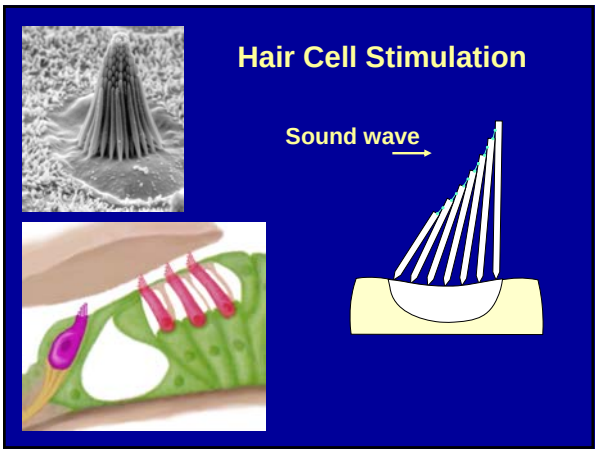
Delayed Onset Cx26 Hearing Loss

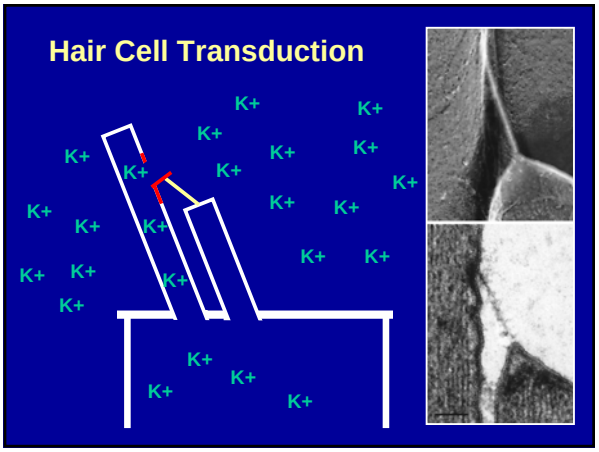
Norris et al. Ear Hear. 27(6):732-741, 2006.
~4% of Cx26 cases pass newborn hearing screens

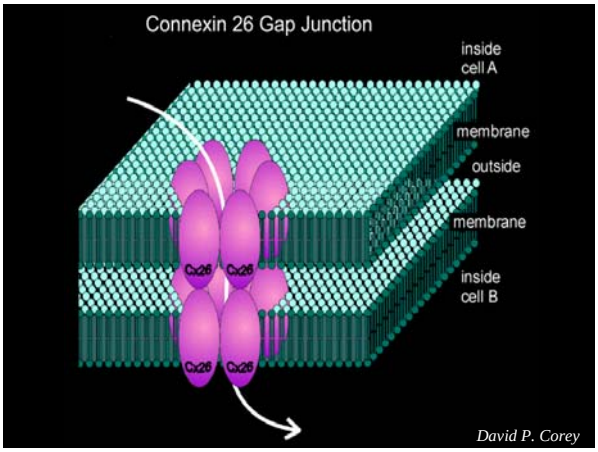
Anatomy of the Human Ear

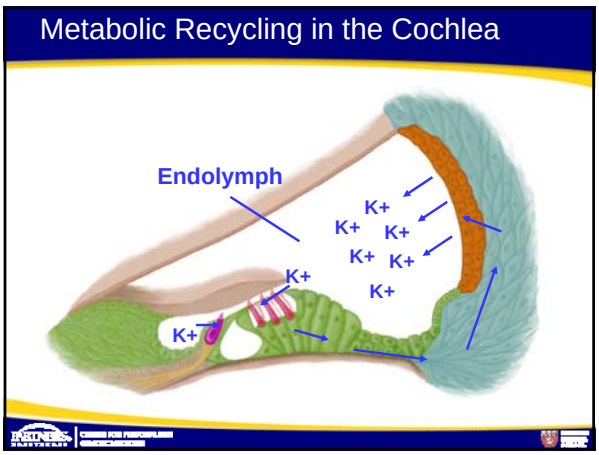




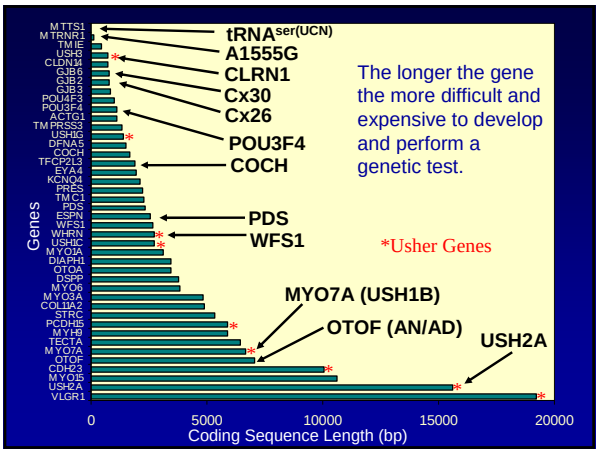






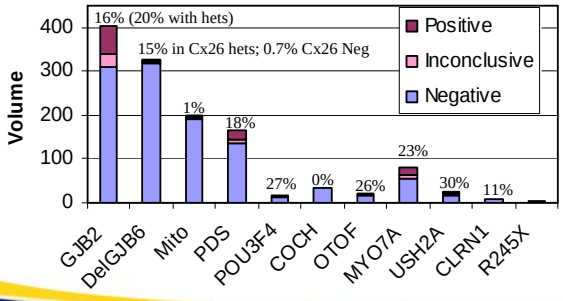


Why is there only a small fraction of genetic tests available for hearing loss when over 50 genes have been identified?



LMM Hearing Loss Test Volume and Yield

679 probands, 1289 tests, 19% positive, 8% inconclusive (mostly hets)



Syndromic Hearing Loss

Syndromes	Gene(s)	
Alport	*COL4A5, COL4A3, COL4A4*	
Branchio-Oto-Renal	*EYA1*	
Jervell and Lange-Nielsen	*KCNQ1, KCNE1/IsK*	Dx with EKG
Mitochondrial (MELAS/MERRF)	*tRNA$^{leu(UUR)}$,tRNA^{lys}*	
Neurofibromatosis type II	*NF2*	
Norrie	*NDP*	
Osteogenesis Imperfecta	*COL1A1, COL1A2*	Dx with CT/MRI and SLC26A4 Genetic Test
Pendred	*SLC26A4 (PDS)*	
Stickler	*COL2A1, COL11A*	
Tranebjaerg-Mohr (DFN1)	*DDP*	
Treacher Collins	*TCOF1*	
Usher	*MYO7A, USH1C, CDH23, PCDH15, SANS, USH2A, GPR98, USH3*	Dx with difficulty!
Waardenburg	*PAX3, MITF, SLUG, EDNRB, EDN3, SOX10*	

There are currently over 400 syndromes with associated hearing loss.

Usher Syndrome Early Diagnosis

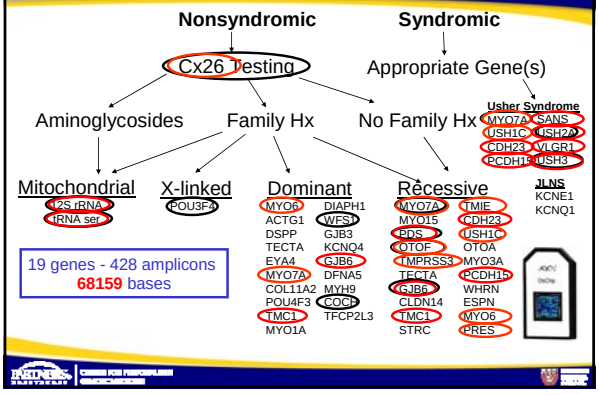
ERG and other ophthalmological exams – may not be positive until adolescence

Vestibular assessment (delayed motor milestones, VEMP, minimized rotation testing, caloric, rotary chair) – test methods are age dependent and not diagnostic for USH1 (not useful for USH2)

- Teschner 2007: 16.2% of deaf children had absent vestibular responses from a new "minimized rotation" test and 50% of them had abnormal ERGs

Genetic testing: not age dependent but may not have conclusive distinction between syndromic vs nonsyndromic prediction if performed early

OtoChip for Hearing Loss and Usher Syndrome



Usher Syndrome Treatment

Vitamin A supplementation

Sunglasses

Gene Therapy:

Acland et al. 2001 successful gene therapy for RP and LCA in dogs

Hashimoto et al. 2007 MYO7A gene therapy in Usher mice

Bainbridge et al. 2008 early human gene therapy trials for LCA

Collaboration with Samuel Jacobson (UPenn): Recruiting positive MYO7A cases for visual function studies in anticipation of gene therapy trials