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A Case Against Perfection
Hearing loss: from detection to treatment

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Medical Genetics & Neurodevelopmental Center

Genetic Breakthroughs

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Genetic Breakthroughs

"Nobody's perfect, but we're working on it."

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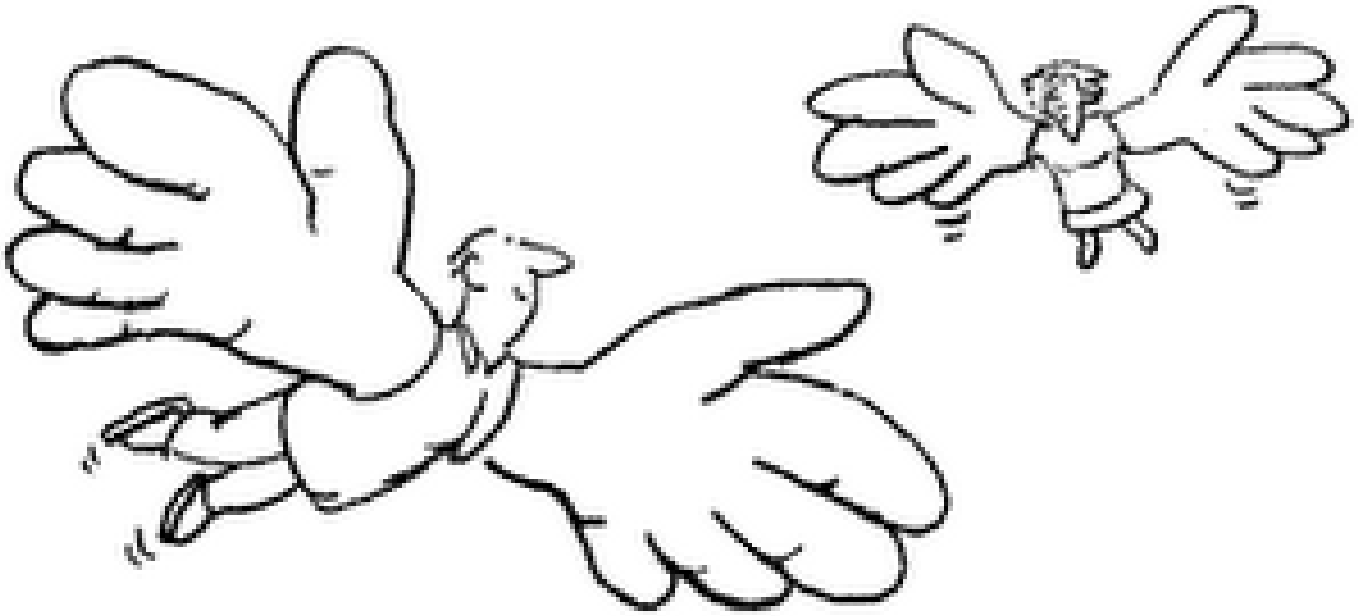

SCIENTISTS ARE HOPING TO ISOLATE A **BIG HAND GENE** TO GIVE PEOPLE THE POWER OF FLIGHT.

chi madden

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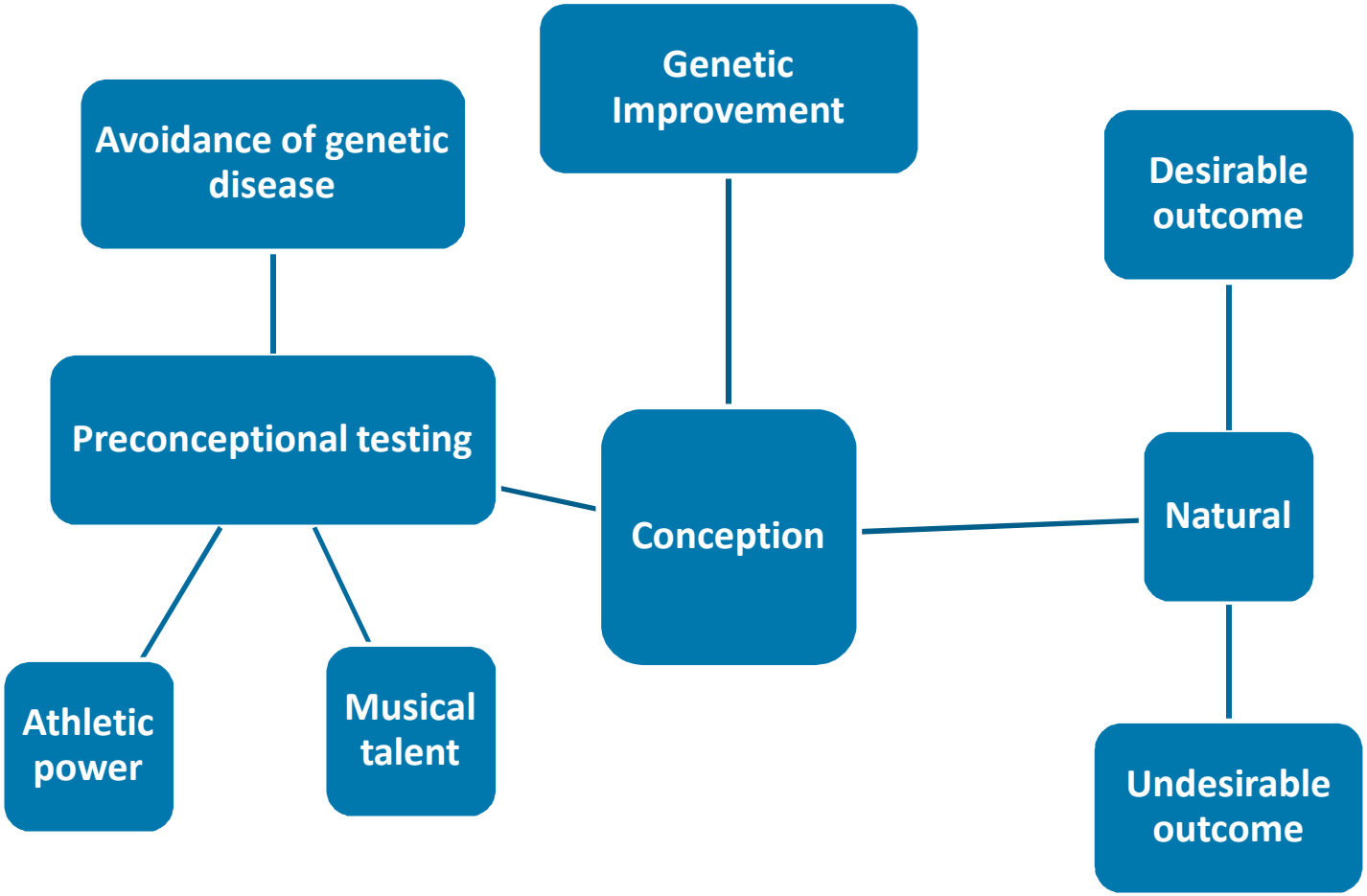

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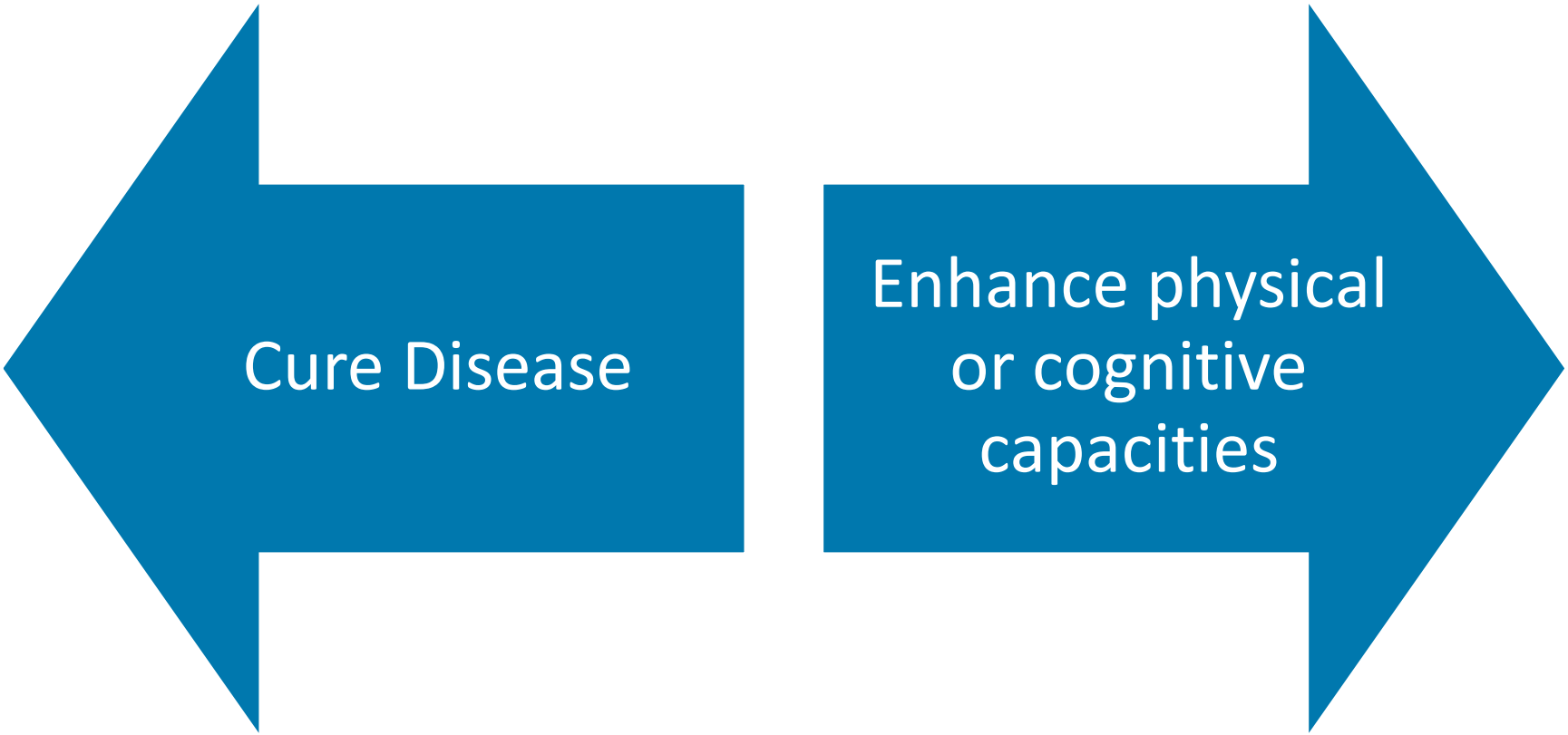
Moral Quandary



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Twenty-four ways to have children

Dr. David D. Weaver and Dr. Luis F. Escobar

American Journal of Medical Genetics
Volume 26, Issue 3, pages 737–740, March 1987

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Hearing Loss Treatment: A Challenging Race

278 Million people world wide suffer from inner ear disorders

The lack of effective treatment is complicated by the diversity of the disease process

Current treatment is limited to medications, surgical intervention and sound amplification

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Epigenetics vs Traditional

Many heritable disorders in humans are caused by DNA sequence changes (mutations) that abolish gene expression

a number of human diseases are caused by inappropriate gene silencing, brought about by epigenetic modifications

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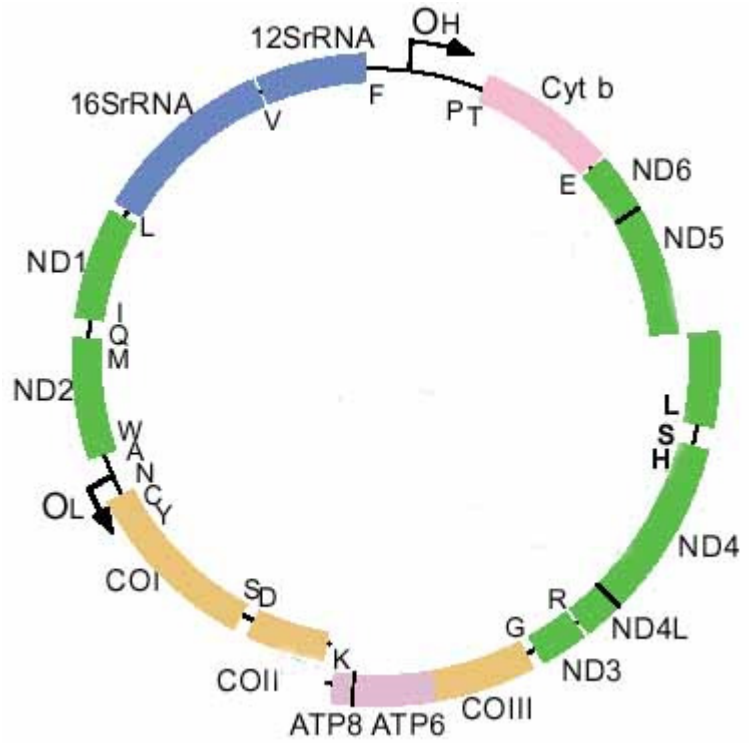
Genetic susceptibility: "A1555G" mitochondrial mutation

Ototoxicity

What does A1555G stand for?

A to G transition at position 1555 in the 12S rRNA gene



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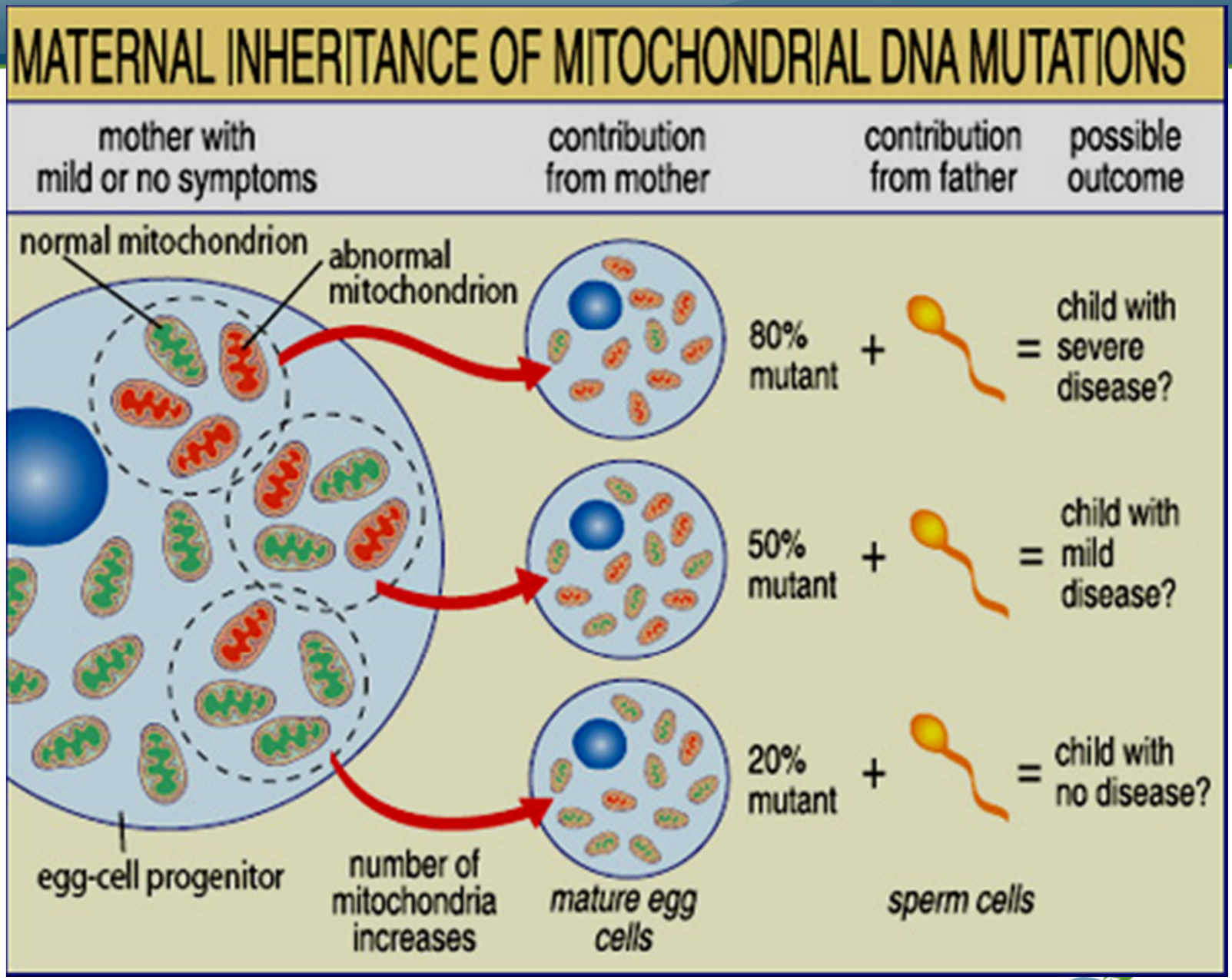
MATERNAL INHERITANCE OF MITOCHONDRIAL DNA MUTATIONS
mother with mild or no symptoms
contribution from mother
contribution from father
possible outcome
normal mitochondrion
abnormal mitochondrion
80% mutant
+
= child with severe disease?
50% mutant
+
= child with mild disease?
20% mutant
+
= child with no disease?
egg-cell progenitor
number of mitochondria increases
mature egg cells
sperm cells

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"A1555G" mitochondrial mutation

Only 17% of individuals present hearing loss after aminoglycoside exposure

Susceptibility to gentamicin or streptomycin ototoxicity

Aust (2001) suggested that children are less prone to develop vestibulotoxicity from gentamicin than adults

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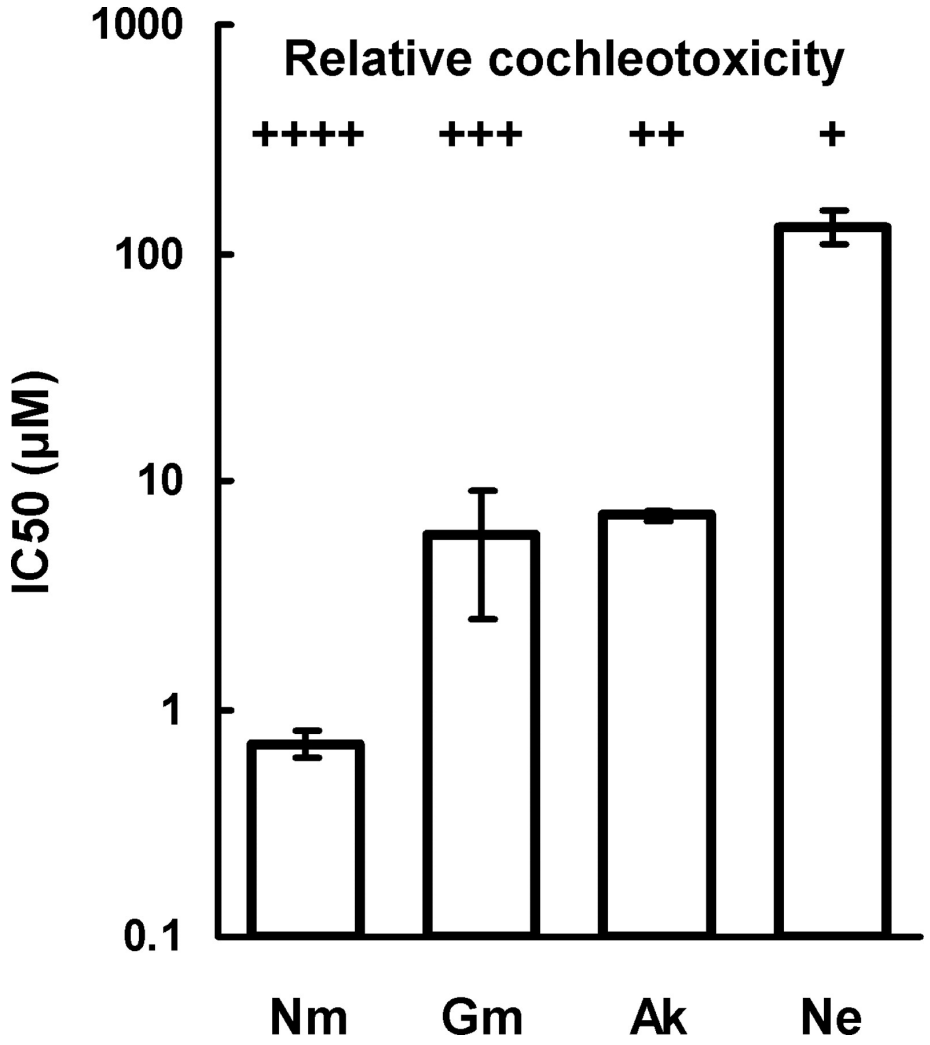
Relationship between inhibition of protein synthesis in mitochondrial hybrid ribosomes and relative in vitro cochleotoxicity of aminoglycoside antibiotics



Hobbie S N et al. PNAS 2008;105:20888-20893

Maternally Inherited Aminoglycoside-Induced and Nonsyndromic Deafness Is Associated with the Novel C1494T Mutation in the Mitochondrial 12S rRNA Gene in a Large Chinese Family

Hui Zhao[1, 2, *], Ronghua Li[1, *], Qiuju Wang[2], Qingfeng Yan[1], Jian-Hong Deng[3], Dongyi Han[2], Yidong Bai[3], Wie-Yen Young[2] and Min-Xin Guan[1, 2,]

[1] Division and Program in Human Genetics and Center for Hearing and Deafness Research, Cincinnati Children's Hospital Medical Center, Cincinnati

[2] Department of Otolaryngology, Head and Neck Surgery, Chinese People's Liberation Army General Hospital, Beijing

[3] Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio

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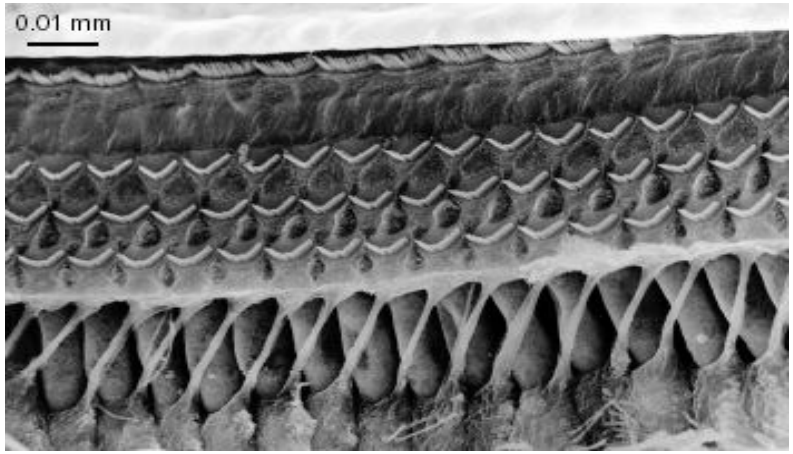
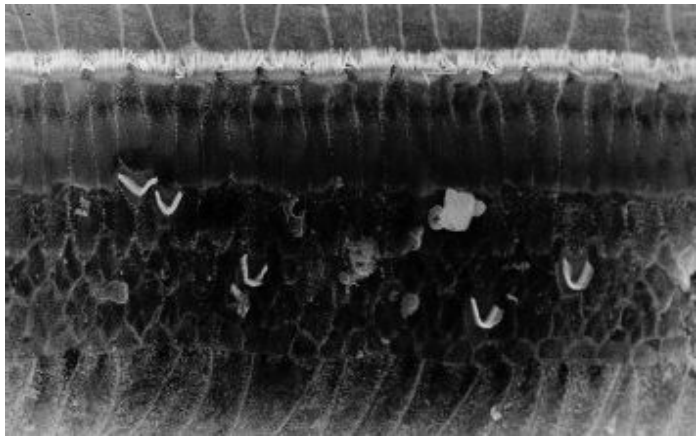
Hair Cell Receptors in the Cochlea





Mechanical vibrations within the cochlea will deflect the hairs, leading to the generation of electrical currents within the hair cells, which give rise to the sensation of hearing.

The hair cells in a guinea pig that had been treated with the antibiotic gentamicin for 10 days

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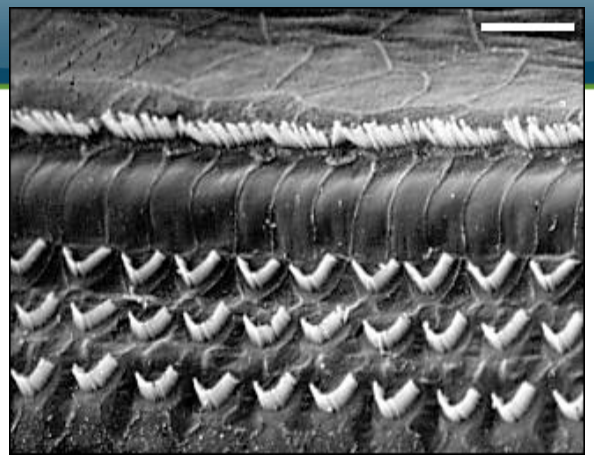
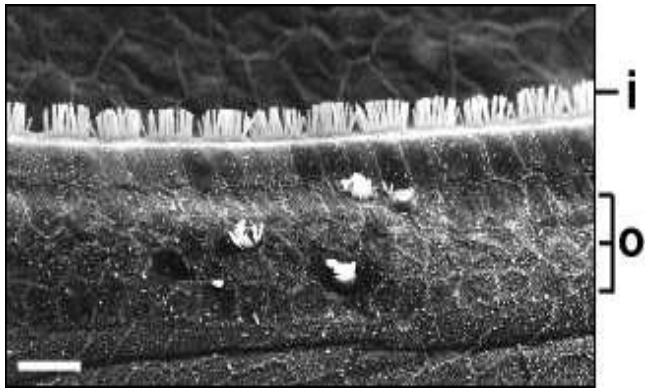
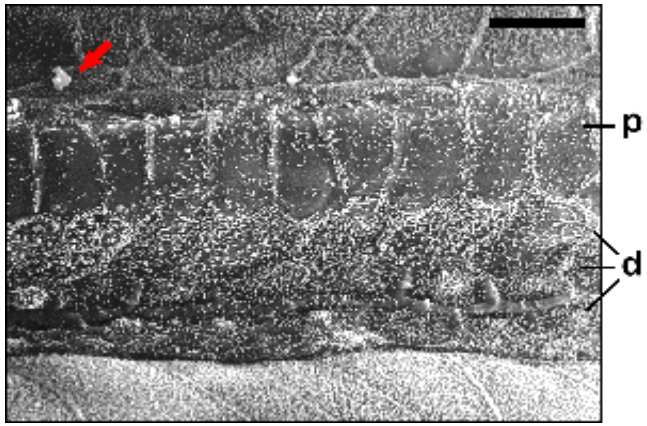
SEM picture of the organ of Corti. Normal organization



At high dosage, the aminoglycoside kills almost all IHC, thus destroying their function (active mechanism).



In humans, such an organ of Corti would show a 60 dB threshold shift and no fine tuning. A hearing aid would restore the gain (loudness),



At even higher doses, all hair cells are missing (red arrow points to two giant stereocilia on a damaged IHC).
This organ of Corti would no longer respond to any sound stimulation.

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Recovery

- Some "sick" inner ear hair cells get better. Nobody knows exactly how many inner ear hair cells are sick rather than being dead
- The brain adapts to the missing inner ear information
- There may be regeneration occuring. Birds can regenerate their hair cells, and although it was felt for a long time that people can't do this, there is a small amount of evidence that some regeneration does occur

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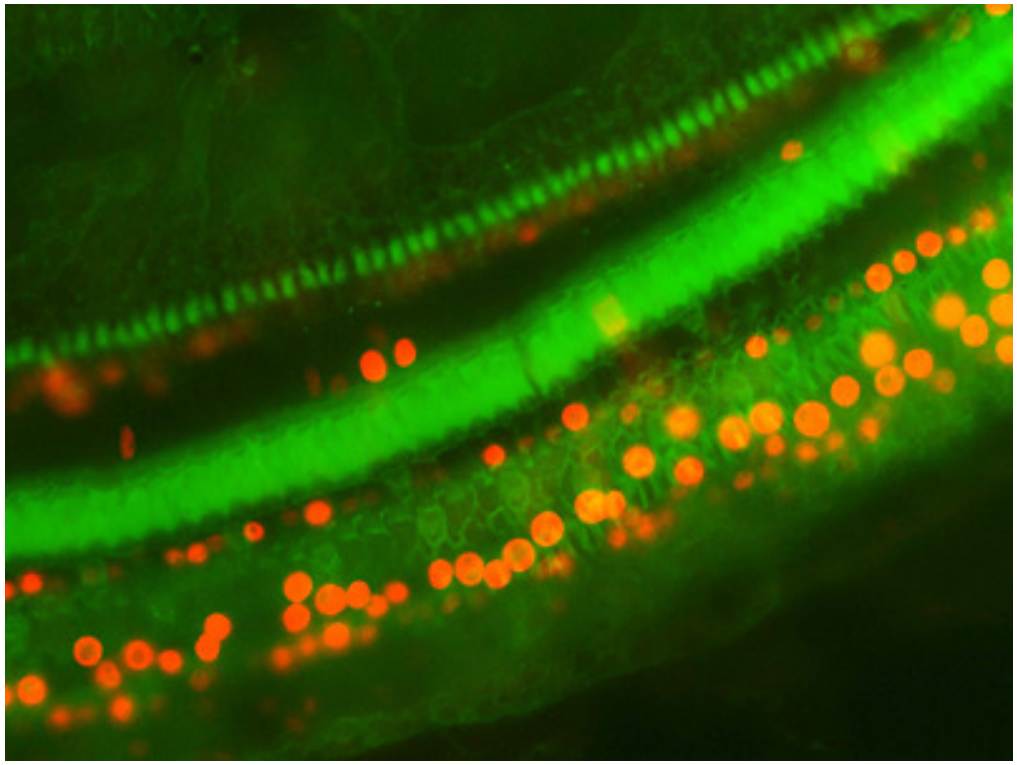
New genes. *Math1* expression (orange) in cells from the inner ear of a guinea pig after gene therapy.



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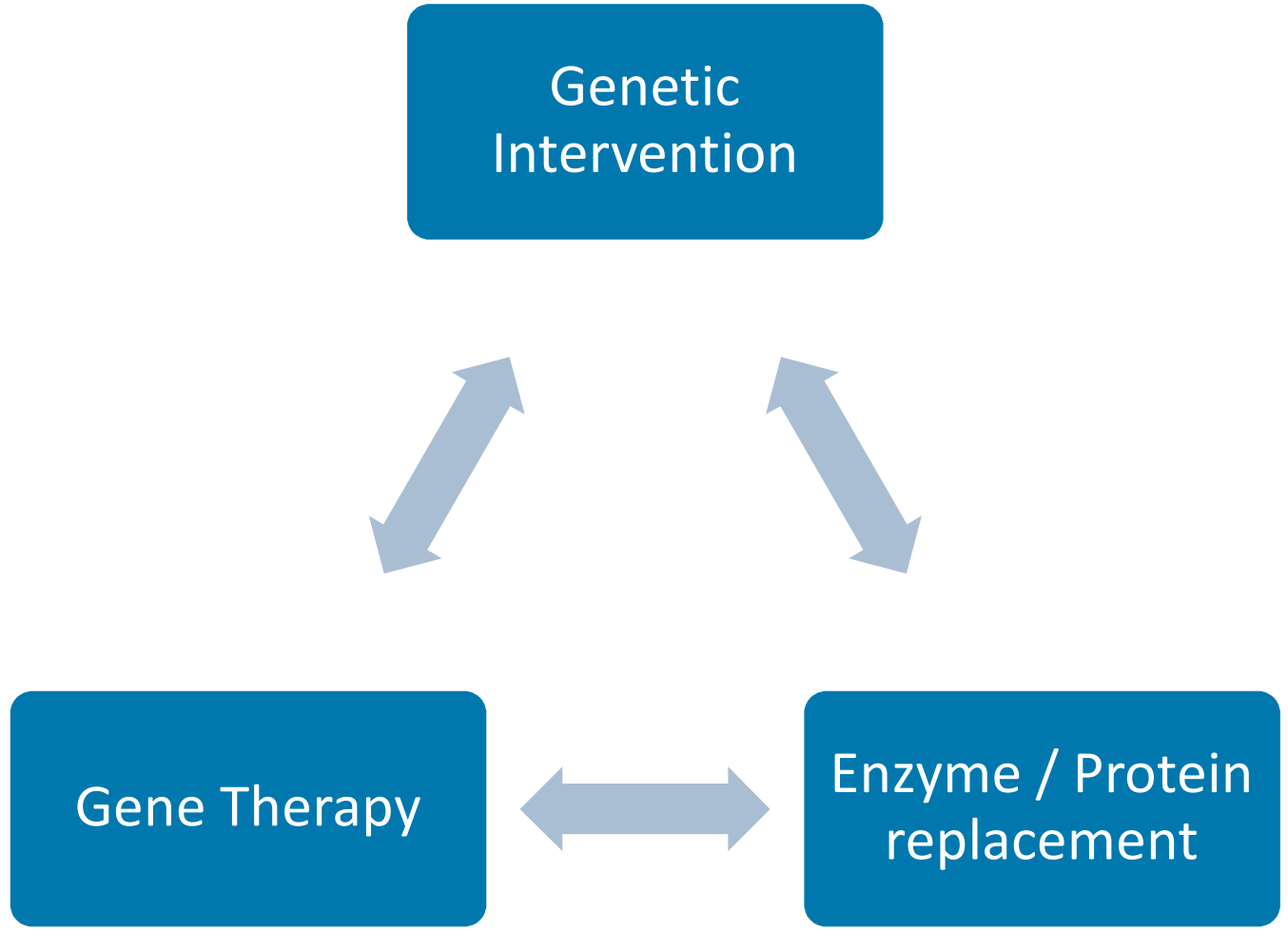

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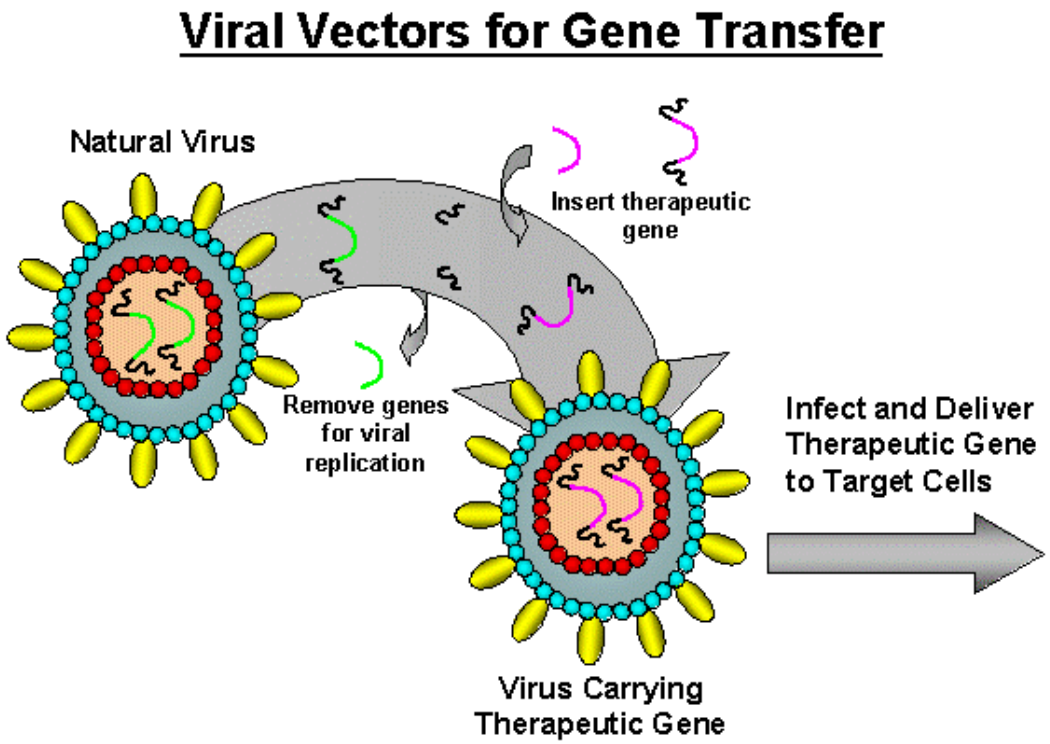
Gene Therapy

Gene transfer is defined simply as a technique to efficiently and stably introduce foreign genes into the genome of target cells



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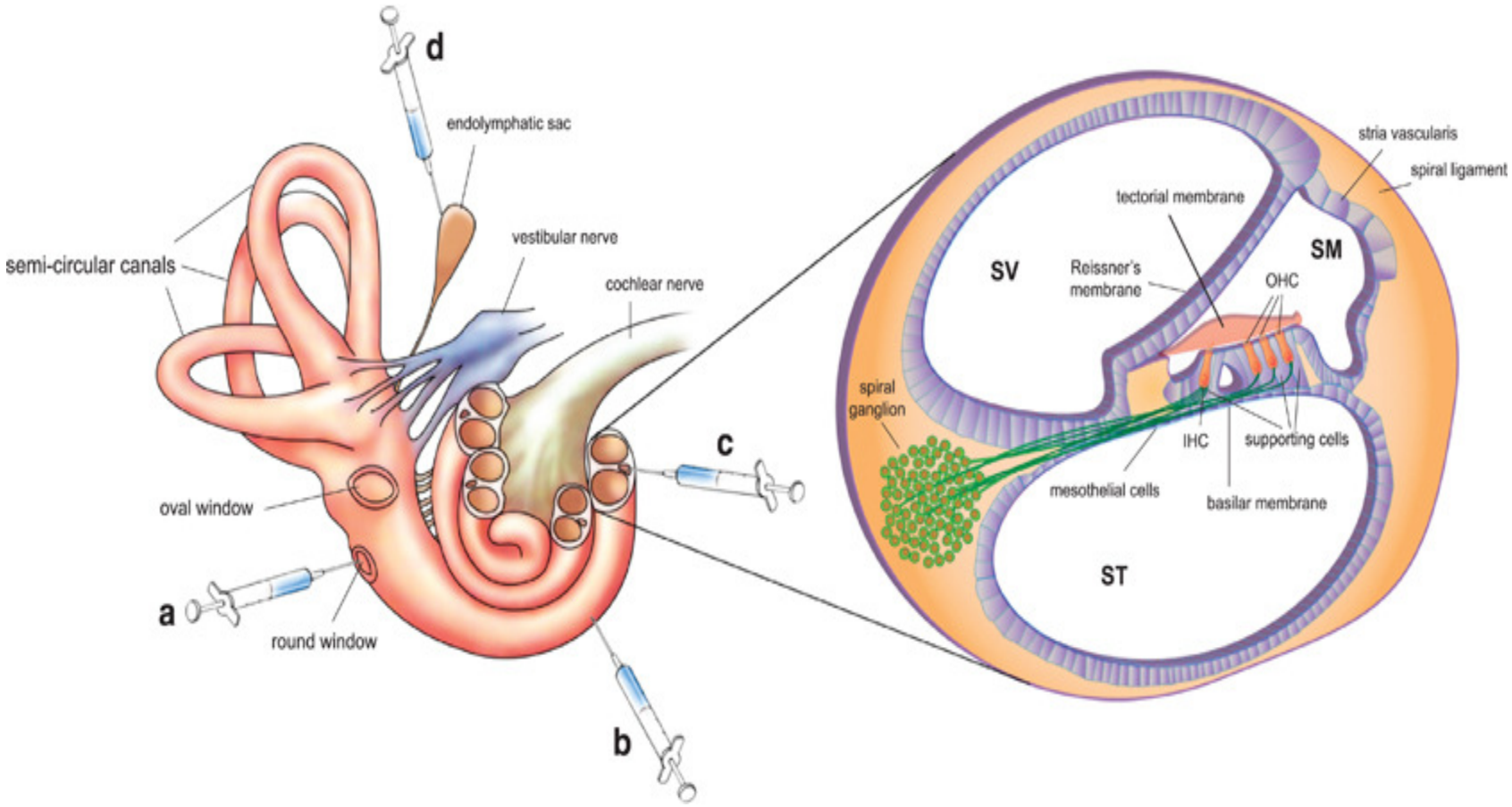
Gene Therapy: Cochleostomy



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Gene Delivery Systems

Vector	Limitations
Adenovirus	Strong host antiviral response with transient expression
Adeno-Associated virus	Difficult to produce high titters, limited gene insert space
Herpes Simplex Virus	Limited duration of transgene recombination
Lentivirus	Ineffcient gene transfection of Hearing cells
Sendal virus	Limited gene insert space

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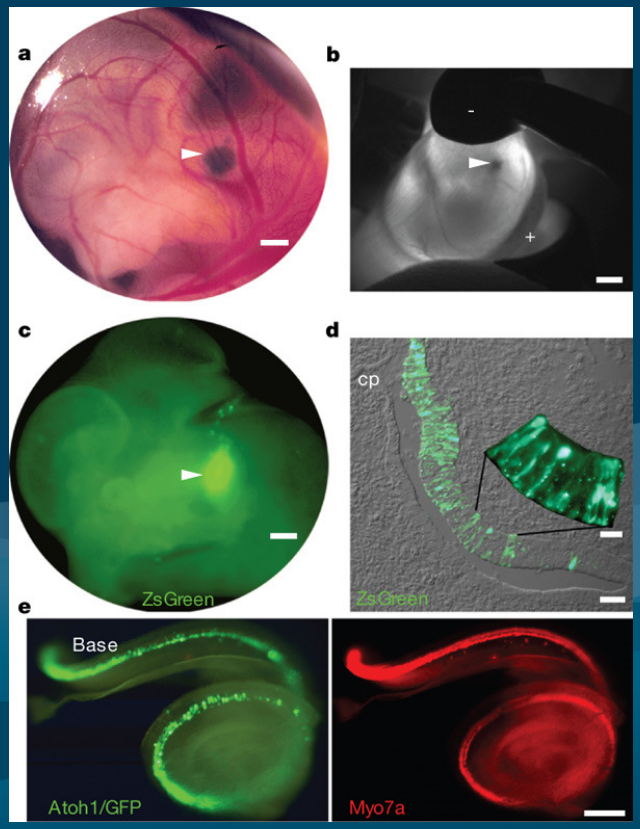
In utero gene transfer to the developing mouse inner ear.

SP Gubbels *et al. Nature* **000**, 1-5 (2008) doi:10.1038/nature07265



a, Expression plasmid was microinjected into the E11.5 otic vesicle. b, The vesicle was centred between the cathode (-) and anode (+) and electroporated. c, Destabilized GFP (ZsGreen) was expressed in the otic territory 24 h after electroporation. d, E12.5 progenitors in the medial and ventral otic epithelium expressed ZsGreen robustly. e, E18.5 ***Atoh1/GFP-transfected cochlea (left) immunostained for Myo7a (right). Arrowheads indicate left otocyst. cp, lateral canal plate; scale bars, 200 m (a); 500 m (b, c); 50 m (d); 10 m (d, inset); 100 m (e).***

Gene Product Treatment

Protein or Other Gene Product Class	Exemplary Proteins or Gene Products
Nerve growth factors	Nerve growth factor (NGF) Neurotrophin-3 Brain-derived neurotrophin factor p70 NT4/5
Structural proteins	Dystrophin Dystrophin-related protein Dystrophin-associated glycoprotein Myosins Actin MERLIN Neurofibronin
Ion Channels	Sodium channel Potassium channel Calcium channel
Cytokines/ Immunoregulatory Protein	Interleukins TGF-α, TGF-β GMCSF
Transcription Factors	Homeobox proteins PAX proteins POU3F4

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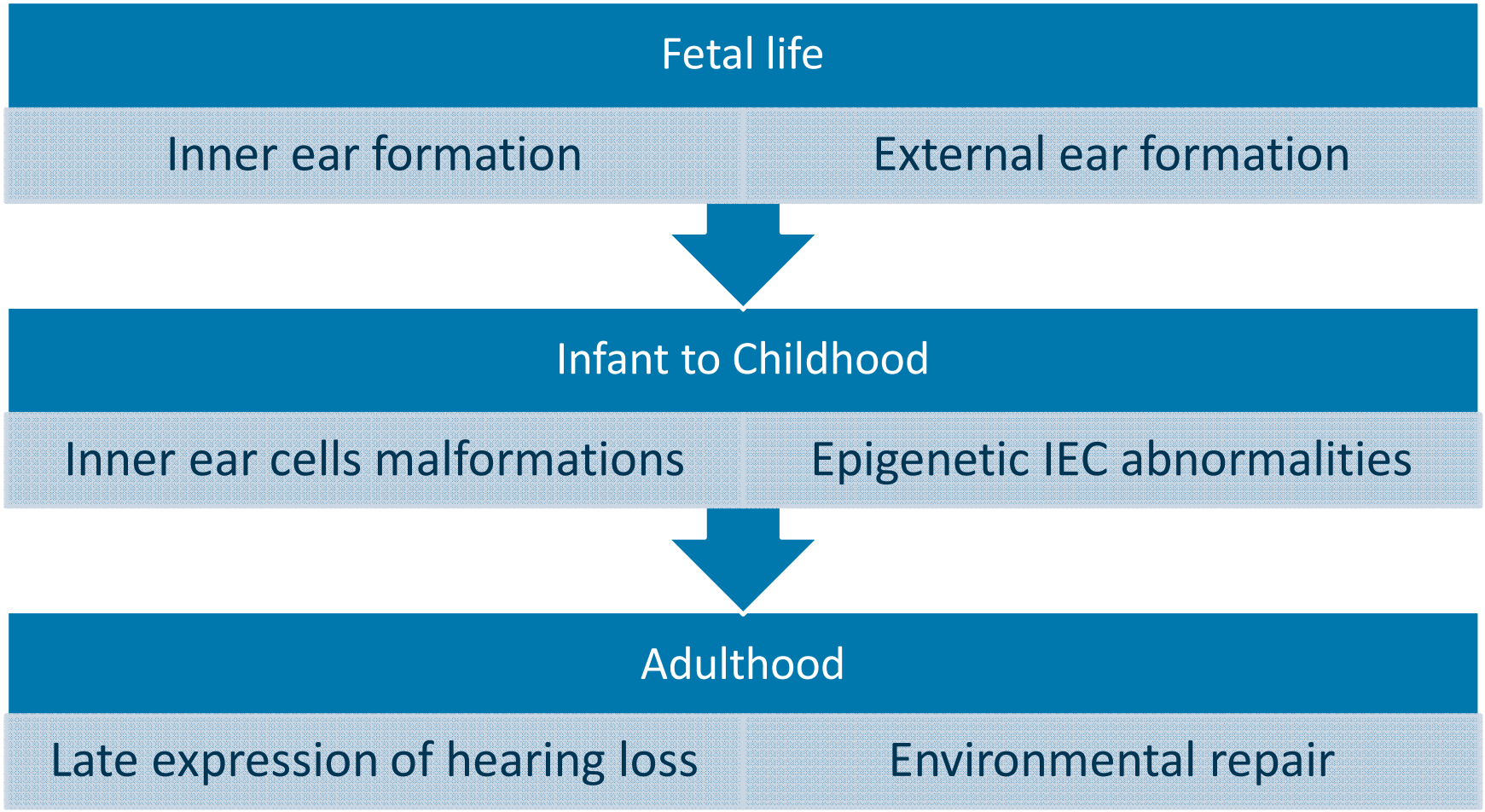
Time of Treatment



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EHDI-Universal hearing screening

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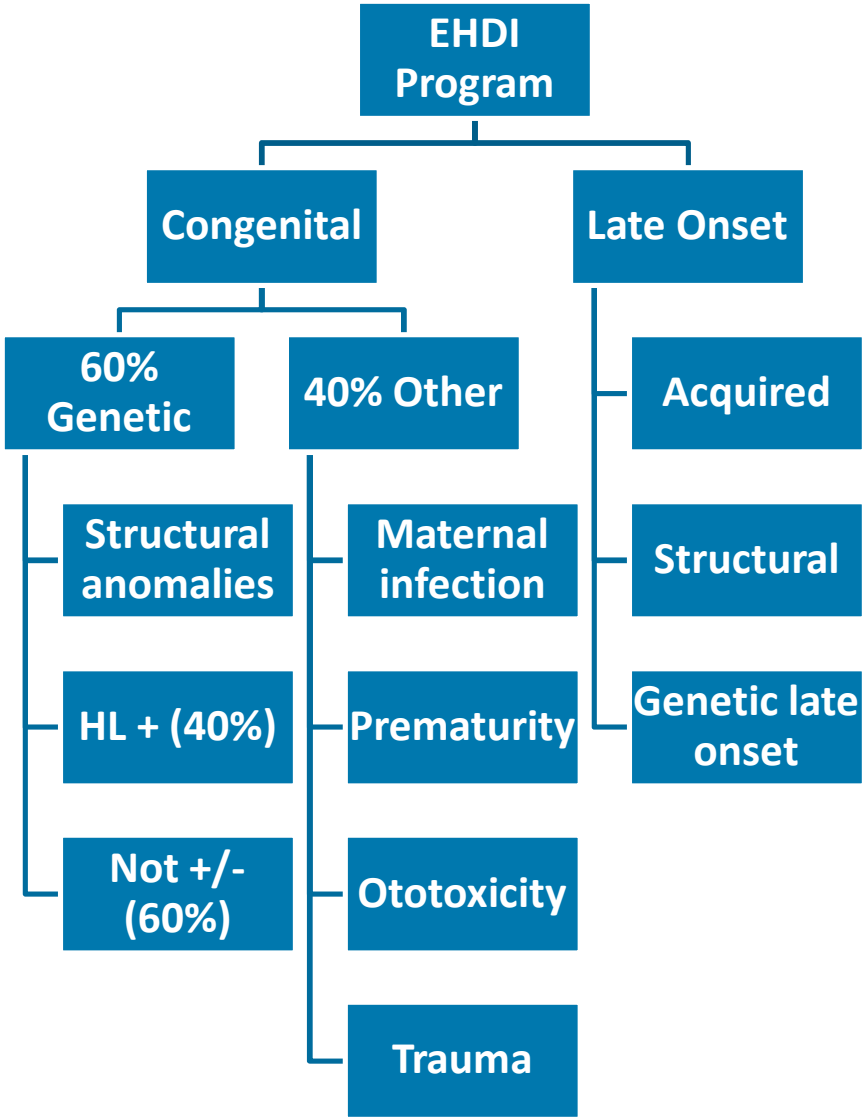

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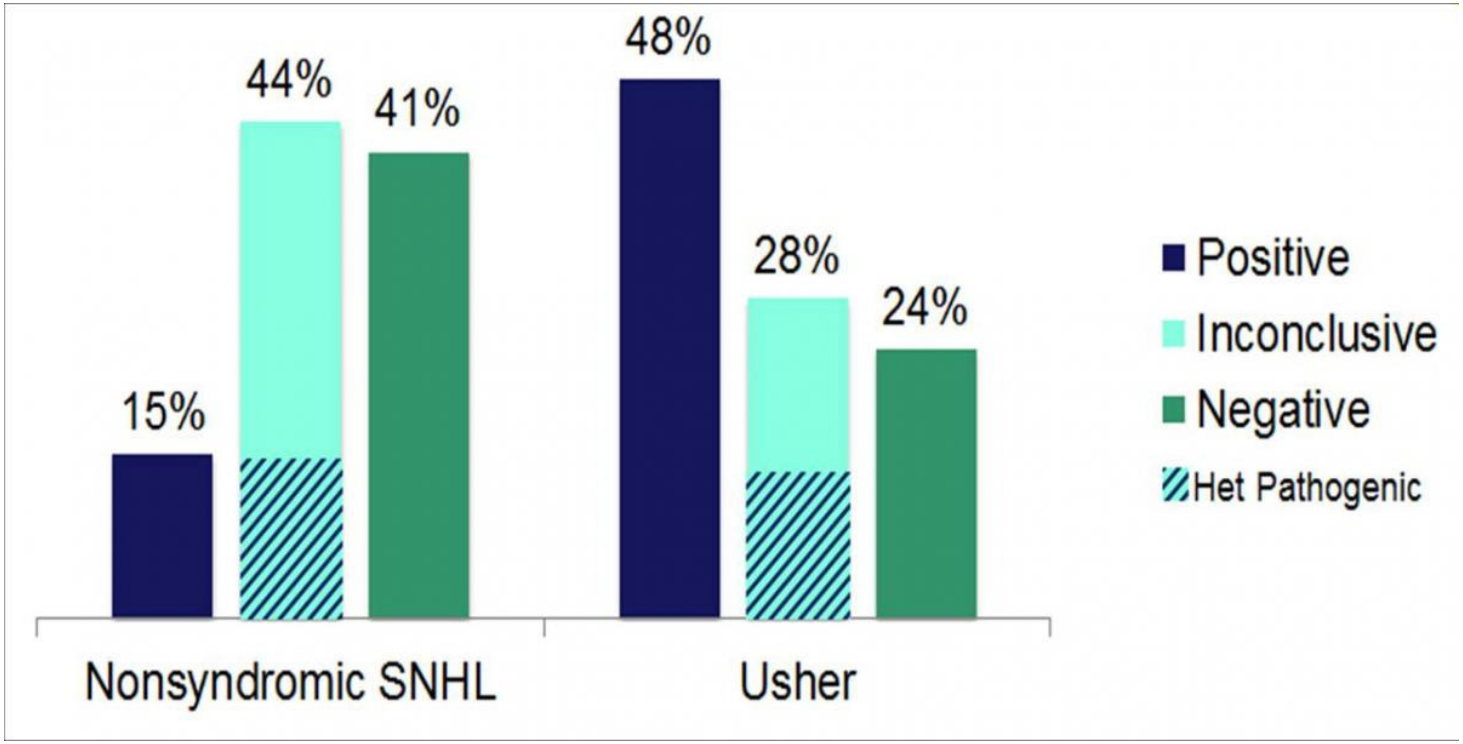
Genetic testing – Genetic Evaluation

OtoChip: 19 genes

OtoGenome: 73 genes

OtoScope: 66 genes



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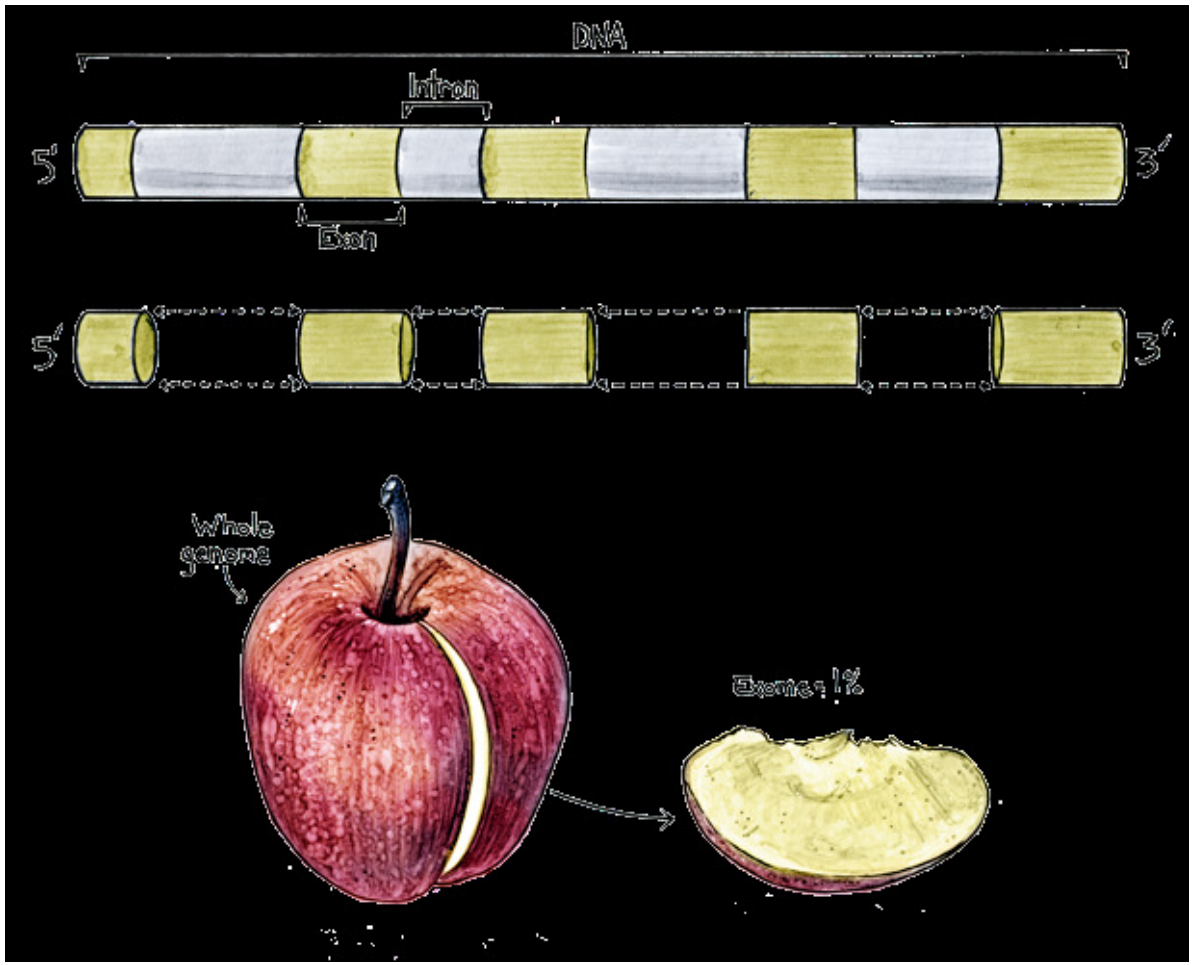
Exome Sequencing



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Deafness in the Genomics Era

A. Eliot Shearer Michael S. Hildebrand Christina M. Sloan Richard J.H. Smith

Hear Res. Dec 2011; 282(1-2): 1–9.

Hearing Loss	Locus / Syndrome	Gene	Number of Families	Targeted region	Sequencer	Reference
ARNSHL	DFNB79	*TPRN*	4	genomic locus	Roche454	(Rehman et al., 2010)
ARNSHL	DFNB82	*GPSM2*	1	whole exome	Illumina GAIIx	(Walsh, et al., 2010b)
ADNSHL	DFNA4	*CEACAM16*	1	whole exome	SOLiD	(Zheng et al., 2011)
XLNSHL	DFNX4	*SMPX*	2	X chromosome	Illumina GAIIx	(Schraders et al., 2011)
Syndromic	Perrault syndrome	*HSD17B4*	1	whole exome	Illumina GAIIx	(Pierce et al., 2010)
Syndromic	Perrault syndrome	*HARS2*	1	genomic locus	Illumina GAIIx	(Pierce et al., 2011)
Syndromic	Carnevale syndrome; Malpuech syndrome; OSA syndrome; Michels syndrome	*MASP1*	2	whole exome	Illumina GAIIx	(Sirmaci et al., 2010)
Syndromic	Hereditary sensory and autonomic neuropathy type 1 (HSAN1) with dementia and hearing loss	*DNMT1*	4	whole exome	Illumina GAIIx; Roche454	(Klein et al., 2011)

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Clinical Process

Genetic Evaluation

Genetic Testing

Improve Diagnosis

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