Newborn Hearing Screening — A Silent Revolution

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Prevalence of hearing loss in Newborns

- Audiologist Marion Downs, 1964
- behavioral hearing screening of neonates
- 17 of 17,000 infants, severe-to-profound bilateral hearing loss

- National Institutes of Health Consensus Development Conference, 1993
- Automated auditory brain-stem response
  - average neural response to a large number of repeated sound signals of the same pitch and intensity
- Otoacoustic emissions
  - sound produced by movements of outer hair cells of the cochlea

- In England, permanent childhood hearing loss
  - bilateral sensorineural loss of 40 dB or more
  - 1.33 per 1000 newborns
- In the United States
  - sensorineural loss of 35 dB or more => referred for confirmatory testing
  - 1.86 per 1000 newborns
  - 2.7 per 1000 children before the age of five years
  - 3.5 per 1000 during adolescence

- Identifying infants who will benefit from early intervention
- Genetic and environmental causes of hearing loss
- Infection
  - acquired immunodeficiency syndrome, South Africa
  - congenital rubella infection, India

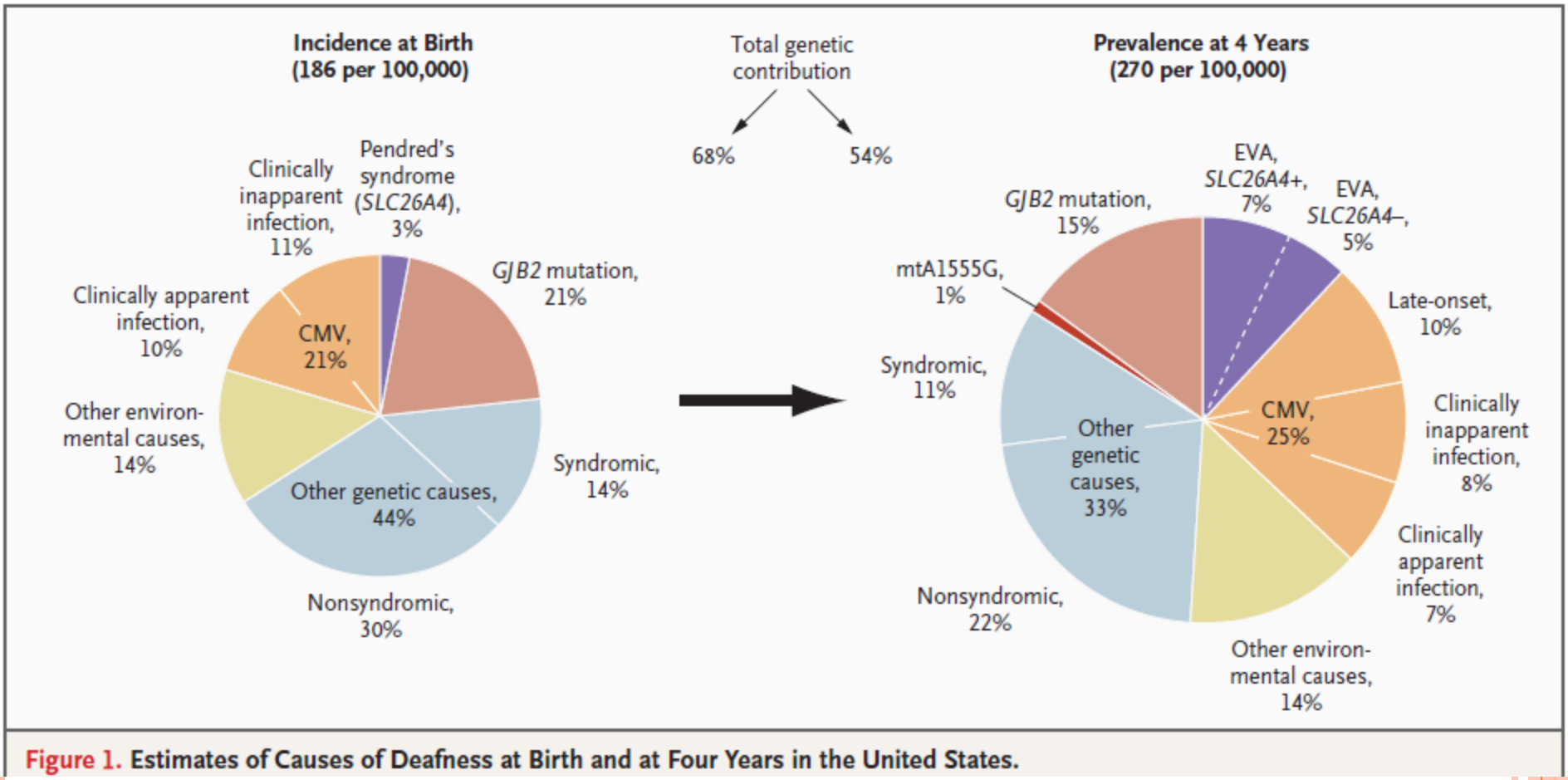


Figure 1. Estimates of Causes of Deafness at Birth and at Four Years in the United States.

Limitations of Existing Screening Programs

- some forms of early-onset hearing loss are not apparent at birth
- the Joint Committee on Infant Hearing
  - 10 risk indicators
  - continued monitoring of hearing status, even if the results of newborn screening are normal

Table 1. Risk Indicators for Audiologic Monitoring for Progressive or Delayed-Onset Sensorineural Hearing Loss, Conductive Hearing Loss, or Both, in Infants (29 Days through 2 Years of Age) with Normal Hearing on Newborn Screening.*

Parental or caregiver concern regarding child's hearing, speech, language, or developmental delay
Family history of permanent hearing loss in childhood
Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss or eustachian-tube dysfunction
Postnatal infections associated with sensorineural hearing loss, including bacterial meningitis
In utero infections such as cytomegalovirus infection, herpes, rubella, syphilis, and toxoplasmosis
Neonatal indicators such as hyperbilirubinemia at a serum level requiring exchange transfusion, persistent pulmonary hypertension of the newborn associated with mechanical ventilation, and conditions requiring the use of extracorporeal-membrane oxygenation
Syndromes associated with progressive hearing loss such as neurofibromatosis, osteopetrosis, and some forms of Usher's syndrome
Neurodegenerative disorders such as Hunter's syndrome or sensory neuropathies such as Friedreich's ataxia and Charcot–Marie–Tooth syndrome
Head trauma
Recurrent or persistent otitis media with effusion for at least 3 months

Genetic Causes of Syndromic hearing loss

- More than 300 forms of syndromic hearing loss
- Pendred’ s syndrome
  - autosomal recessive
  - two *SLC26A4* mutations
  - 61% with nonsyndromic enlargement of the vestibular aqueduct are found to carry a single mutation

- transport of iodide across the thyrocyte is defective => thyromegaly
- Mondini malformations
- enlargement of the vestibular aqueduct

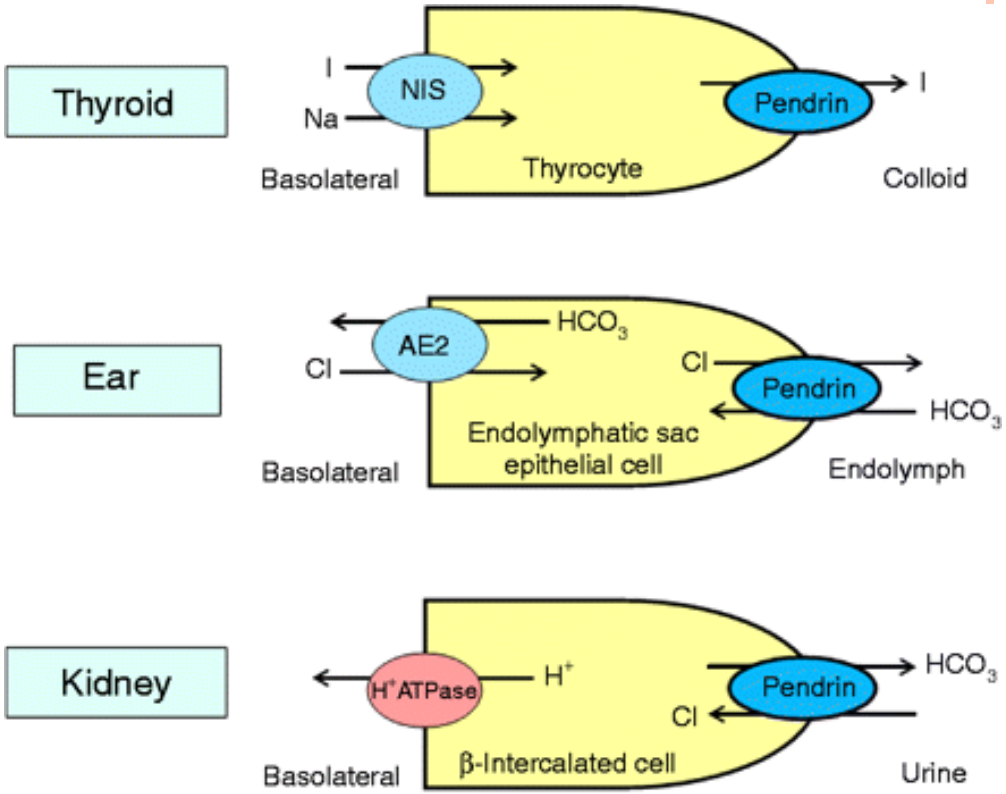


Table 2. Selected Forms of Syndromic Hearing Loss.*

Disorder	Features	Pattern of Inheritance	Relative Frequency†‡	No. of Loci	Comments	OMIM No.
Alport's syndrome	Hematuria with progressive renal failure, progressive late-onset high-frequency sensorineural hearing loss; anterior lenticonus and macular flecks	X L or A R	1%	3	Results from mutations in 1 of 3 collagen genes expressed in glomerular basement membrane COL4A3,COL4A4, COL4A5	301050
Alström's syndrome	Truncal obesity beginning in childhood; progressive retinal dystrophy involving cones and rods; type 2 diabetes; progressive sensorineural hearing loss, acanthosis nigricans, and cardiomyopathy can begin in infancy	A R	Common in Acadians of Nova Scotia and Louisiana	1	Results from mutations involving *ALMS1* at 2p13, discovered at the breakpoint of a chromosomal translocation; *ALMS1* expressed ubiquitously at low levels and encodes a 4169–amino acid protein of unknown function	203800
Type 4 Bartter's syndrome	Polyhydramnios and prematurity with metabolic acidosis and high renin and aldosterone levels, with salt wasting, normal blood pressure, and renal failure; caused by mutations in the chloride-channel genes *BSND*, *CLCNKA*, and *CLCNKB* expressed in the kidney and stria vascularis	A R or digenic	Most common in consanguineous Middle Easterners	3	Three genes acting alone or in combination; *CLCNKB* deletions from unequal crossing-over; digenic homozygotes for mutations of both *CLCNK* loci have been described; murine knockouts exhibit nephrogenic diabetes	602522 602023 602024
Biotinidase deficiency	Seizures; hypotonia; ataxia; organic acidemia; alopecia associated with sensorineural hearing loss; in 75% of affected patients	A R	1/60,000‡	1	One of metabolic diseases screened for at birth in many states; preventable form of hearing loss with prompt biotin supplements	253260
Branchio-oto-renal (BOR) syndrome	Hearing loss; preauricular pits; malformed pinnae; branchial fistulae; renal anomalies ranging from structural malformations to agenesis	AD	2%	1	BOR (*EYA1*) gene product interacts with 128 other proteins; defects in several lead to somewhat similar syndromes	113650
DFNA17	Sensorineural hearing loss; with or without nephritis; cataracts; platelet anomalies; leukocyte inclusions; hemorrhagic tendency	AD	Rare	1	*MYH9* mutations can cause dominant Alport's syndrome with features of Fechtner's syndrome or Sebastian syndrome, or isolated sensorineural hearing loss	603622
DFNA22	Dominant mutations of *MYO6* can cause a progressive postlingual sensorineural hearing loss associated with hypertrophic cardiomyopathy, sudden death, arrhythmias, and long-QT interval	AD	Rare	1	*MYO6* expressed in heart and cochlea, participates in intracellular transport, anchoring of organelles, or both; other mutations cause DFNA22, a form of nonsyndromic sensorineural hearing loss	606346
Fabry disease	Vascular skin lesions; abdominal pain; nephropathy with renal failure; corneal dystrophy; angina; cardiomyopathy, high-frequency sensorineural hearing loss; treatment by renal transplantation or enzyme replacement	XL	1/40,000‡	1	Deficiency of α-galactosidase; high-frequency sensorineural hearing loss; in 78% of cases progressive or sudden onset; may have isolated cardiomyopathy, arrhythmia, and sudden death	301500

Jervell and Lange–Nielsen syndrome	Profound sensorineural hearing loss with prolongation of QT interval, syncope, and risk of sudden death	AR	0.25–0.5%	2	Genes encode subunits of potassium channels; carriers also at risk for sudden death; treatment effective	220400
Nance deafness	Congenital fixation of stapes foot plate with mixed hearing loss; distinctive CT findings of dilated internal auditory canal and poor separation of basal cochlear turn	XL	>1%	1	Gene defects in *POU3F4*, which encodes a DNA-binding transcription factor; deletions common; perilymphatic "gusher" often complicates stapes surgery; mild hearing loss in some female carriers	304400
Pendred's syndrome	Sensorineural hearing loss; goiter; cochlear malformations; high risk of nonsyndromic enlarged vestibular aqueduct in carriers, which is seen in 20% of children with late-onset hearing loss	AR	4–10%	1	Iodine transport defect diagnosed by perchlorate discharge test in those homozygous for Pendred's syndrome (*SLC26A4*); sensorineural hearing loss with variable onset and severity	274600
Renal tubular acidosis	Dehydration, growth failure, metabolic acidosis with alkaline urine, nephrocalcinosis and rickets; variable hearing loss	AR, frequent consanguinity	Found in inbred North Africans	>2	Defects in proton-pump genes *ATP6B1* or *ATP6N1B* expressed in kidney and stria vascularis; additional loci probable	267300 602722
Treacher Collins syndrome	Conductive hearing loss with malformed ossicles, microtia, cleft palate; micrognathia, downward slanting eyes, coloboma of the eyelid	AD	1%	1	Frequent absence of a family history possibly reflecting new mutations or mild expression in a parent	154500
Usher's syndrome	Sensorineural hearing loss; vestibular symptoms; retinitis pigmentosa		4–6%	12	Commonest cause of deafness with blindness; early diagnosis of retinitis pigmentosa possible with electroretinography; cochlear implants effective; sign language recommended because eventual blindness may require finger spelling; some mutations cause only sensorineural hearing loss	Type 1, 276900, 276904, 601067
	Type 1, profound hearing loss; vestibular symptoms; retinitis pigmentosa beginning in first decade	AR	(60)	7		602097, 602083, 606943
	Type 2, stable moderate-to-severe hearing loss; retinitis pigmentosa in first to second decade	AR	(30)	4		Type 2, 276901, 276905, 605472
	Type 3, progressive hearing loss; variable vestibular symptoms; variable onset of retinitis pigmentosa	AR	(10)	1		Type 3, 276902
Waardenburg's syndrome	Neural crestopathy with hearing loss in one or both ears; patches of eye, skin, hair hypopigmentation; occasional Hirschsprung's disease, spina bifida		1–4%	9	Hearing loss caused by defective migration of pigment cells to stria vascularis; infrequent bowel movements common; Hirschsprung's disease with obstruction or gastrointestinal dyskinesia seen; *WS* genes include hierarchy of regulatory and structural genes controlling migration and function of neural-crest cells	Type 1, 193500
	Type 1, white forelock; dystopia canthorum; synophoris; pinched nares	AD	Common	1		Type 2, 193510
	Type 2, dystopia absent	AD or AR	Less common	4		600193, 600193, 608890
	Type 3, limb defects in *WS1* homozygotes	AD	Very rare	1		Type 3, 148820
	Type 4, increased incidence of Hirschsprung's disease in carriers and homozygotes	AR	Rare	3		Type 4, 277580

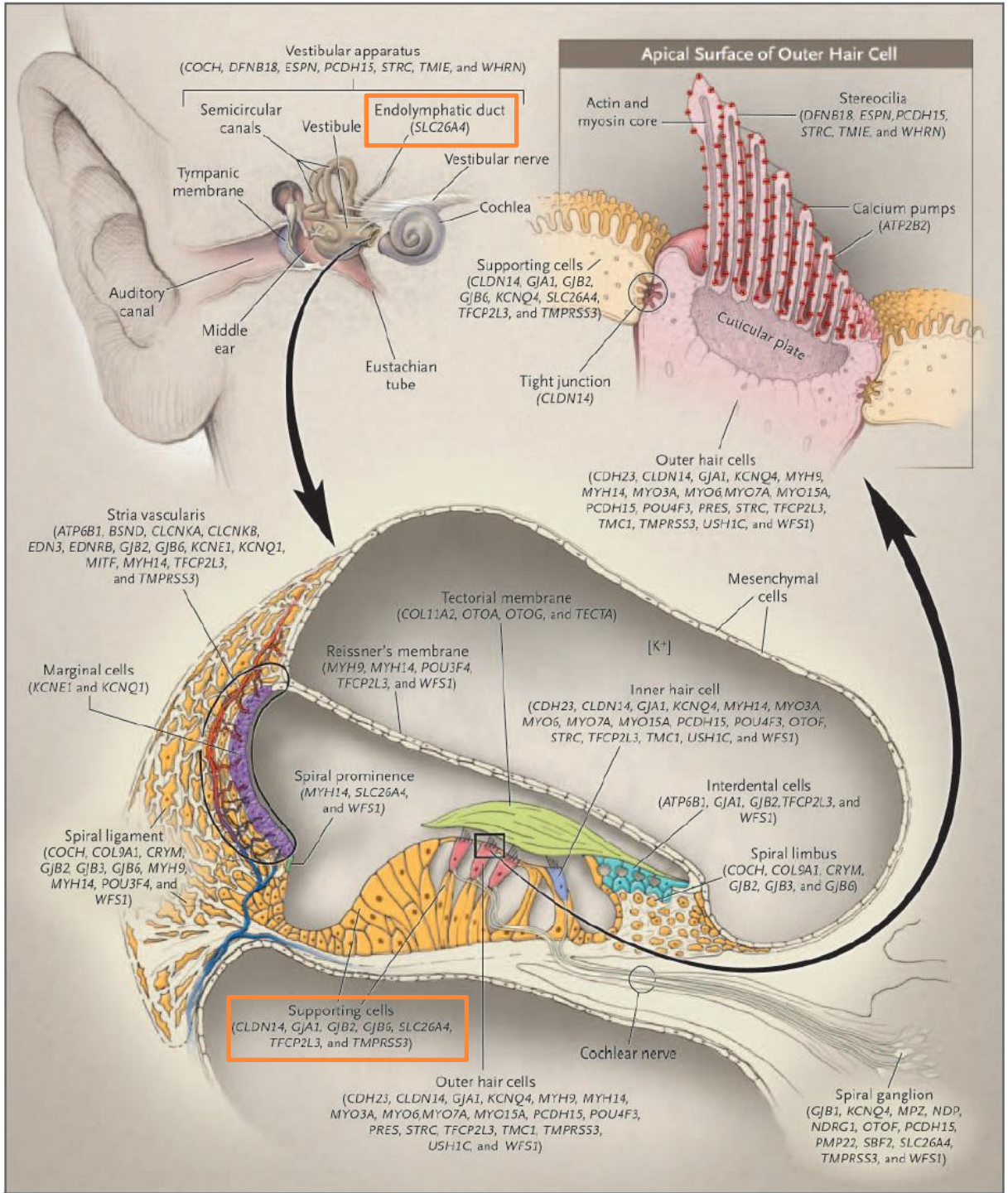
Genetic Causes of Nonsyndromic hearing loss

- Most cases of genetic hearing loss are nonsyndromic
  - more than 110 chromosomal loci and at least 65 genes
- DFNA: autosomal dominant
- DFNB: autosomal recessive
- DFNX: X-linked

- *GJB2,* account for 30 to 50 percent of all cases of profound nonsyndromic hearing loss
- connexin 26
  - gap-junction protein expressed in supporting cells and connective tissues of the cochlea
  - form intercellular channels allowing recycling of potassium ions

- Most cases of genetic deafness result from mutations involving a single gene
- a small number in which hearing loss is determined by mutations in two independent genes
- DFNB1
  - two mutations involving *GJB2*
  - two mutations in *GJB6*
  - Combination of mutations involving both genes
- GJB6
  - connexin 30, gap-junction channels with connexin 26 subunits

- Mating pattern of deaf persons who communicate by sign language
- very high frequency of marriages among the deaf
- brings together rare deafness genes of all types with a much greater frequency


Vestibular apparatus
(COCH, DFNB18, ESPN, PCDH15, STRC, TMIE, and WHRN)
Semicircular canals
Vestibule
Endolymphatic duct
(SLC26A4)
Vestibular nerve
Tympanic membrane
Cochlea
Auditory canal
Middle ear
Eustachian tube
Apical Surface of Outer Hair Cell
Actin and myosin core
Stereocilia
(DFNB18, ESPN, PCDH15, STRC, TMIE, and WHRN)
Calcium pumps
(ATP2B2)
Supporting cells
(CLDN14, GJA1, GJB2, GJB6, KCNQ4, SLC26A4, TFCP2L3, and TMPRSS3)
Cuticular plate
Tight junction
(CLDN14)
Outer hair cells
(CDH23, CLDN14, GJA1, KCNQ4, MYH9, MYH14, MYO3A, MYO6,MYO7A, MYO15A, PCDH15, POU4F3, PRES, STRC, TFCP2L3, TMC1, TMPRSS3, USH1C, and WFS1)
Stria vascularis
(ATP6B1, BSND, CLCNKA, CLCNKB, EDN3, EDNRB, GJB2, GJB6, KCNE1, KCNQ1, MITF, MYH14, TFCP2L3, and TMPRSS3)
Tectorial membrane
(COL11A2, OTOA, OTOG, and TECTA)
Mesenchymal cells
[K+]
Reissner's membrane
(MYH9, MYH14, POU3F4, TFCP2L3, and WFS1)
Marginal cells
(KCNE1 and KCNQ1)
Inner hair cell
(CDH23, CLDN14, GJA1, KCNQ4, MYH14, MYO3A, MYO6, MYO7A, MYO15A, PCDH15, POU4F3, OTOF, STRC, TFCP2L3, TMC1, USH1C, and WFS1)
Spiral prominence
(MYH14, SLC26A4, and WFS1)
Interdental cells
(ATP6B1, GJA1, GJB2,TFCP2L3, and WFS1)
Spiral ligament
(COCH, COL9A1, CRYM, GJB2, GJB3, GJB6, MYH9, MYH14, POU3F4, and WFS1)
Spiral limbus
(COCH, COL9A1, CRYM, GJB2, GJB3, and GJB6)
Supporting cells
(CLDN14, GJA1, GJB2, GJB6, SLC26A4, TFCP2L3, and TMPRSS3)
Cochlear nerve
Outer hair cells
(CDH23, CLDN14, GJA1, KCNQ4, MYH9, MYH14, MYO3A, MYO6,MYO7A, MYO15A, PCDH15, POU4F3, PRES, STRC, TFCP2L3, TMC1, TMPRSS3, USH1C, and WFS1)
Spiral ganglion
(GJB1, KCNQ4, MPZ, NDP, NDRG1, OTOF, PCDH15, PMP22, SBF2, SLC26A4, TMPRSS3, and WFS1)

Environmental Causes of Prelingual Hearing Loss

- Congenital cytomegalovirus infection has replaced rubella embryopathy as the most prevalent cause
  - 10 percent of infants with congenital hearing loss
  - 35 percent of moderate-to-severe late-onset loss
- incidence of the infection in newborns: 0.1-2%
- hearing loss is present at birth in 3.9% of all infants with the virus
  - unilateral, fluctuating, or progressive in nature
  - onset can be delayed for months or even years

- Pharmacologic ototoxicity is another important environmental cause
- 10% have mutations involving the mitochondrial 12S ribosomal (rRNA) gene
  - A1555G substitution
  - extreme sensitivity to aminoglycoside ototoxicity
  - prevalence: one in 20,000 to 40,000 births

Improving Detection of Late-Onset Prelingual Hearing Loss

- Audiologic screening cannot detect forms of deafness that are not expressed at birth
- molecular genetic tests on blood spots from all newborns
  - risk for the most frequent causes of late-onset loss
  - continued audiologic monitoring
- Tests for *GJB2* deafness, mitochondrial A1555G mutation, *SLC26A4* are commercially available
- cytomegalovirus

- from detection of hearing loss to the identification of its cause
  - disease prevention
  - improved therapy
  - improved interpretation of the results of early intervention
  - psychological benefits of understanding the true cause of a disease

- Successful induction of hair-cell regeneration in guinea pigs
- Gene silencing by RNA interference in the mouse
  - specific forms of genetic deafness in humans may someday be addressed by similar forms of gene therapy
- use of molecular diagnostic DNA chips already being developed
  - routine, simultaneous testing for mutations involving many genes

- Newborn hearing screening
- standardization of testing protocols
- immediate confirmation of abnormal screening tests
- introduction of an etiologic focus
- improved identification of infants at risk for late-onset prelingual hearing loss

- Thanks for your attention.