Genetic Bases of Hearing Loss: Future Treatment Implications

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1. Review Basic Concepts and Ideas

2. Review Gene Involvement in Hearing and Auditory organs development

3. Review some of the future forms of treatment involving hearing loss

4. Review the importance of recognizing that genetic testing does not equal to genetic evaluation

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Special Needs

Used in clinical diagnostic and functional development to describe individuals who require assistance : medical, mental, or psychological

Special needs often refers to special needs within an educational context. This is also referred to as special educational needs (SEN).

In Germany a similar term exists. Special needs children are called "besondere Kinder" ("special children").

Special Needs

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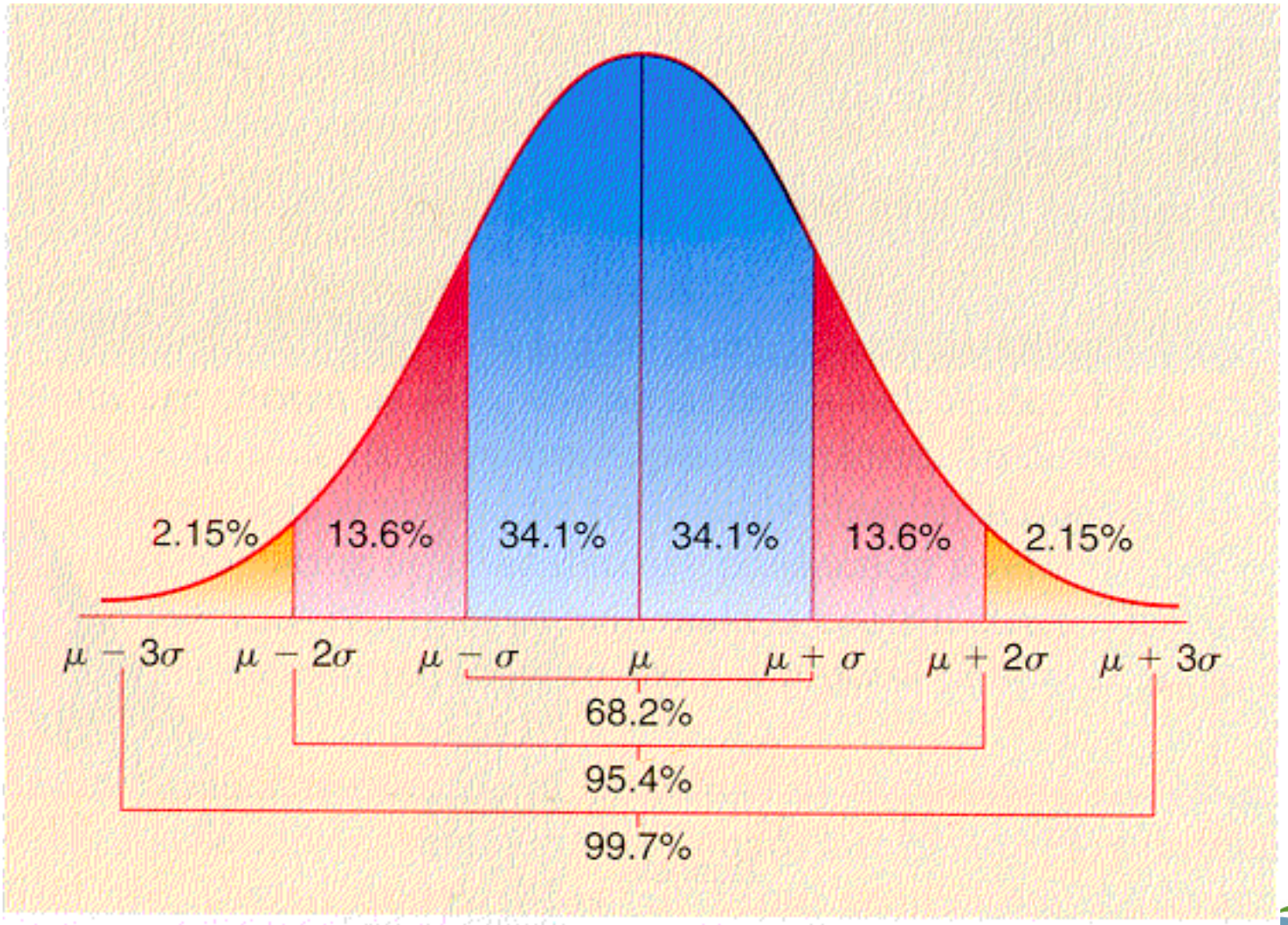
Establishment of a System



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Medical Special Needs in the US

http://www.cdc.gov/nchs/data

19% of Americans are classified as a person with a special need, which equals the population of the states of FL and CA combined

41% of children with developmental difficulties have multiple special needs

17% of Americans will experience a communication disorder at some point in their life, which includes sensing, interpreting and responding (i.e. auditory processing disorder).

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Medical Genetics

20-40%

- Of Children with hearing loss have other disabilities

900

- Genetic conditions have been described to include hearing loss and other special needs

802

- Conditions have been described to present with deafness

Isolated hearing loss may not be the most common form of hearing loss in the future

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Other Diagnoses Associated with Hearing Loss

Gallaudet Research Institute, 2003

Diagnosis	%
Learning difficulties	10.7
Developmental delay	9.8
Attention difficulties	6.6
Blindness and low vision	3.9
Cerebral palsy	3.5
Emotional disturbance	1.5
Other conditions	12.1
TOTAL	**48.1**

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Genetics: A case against perfection

"Congratulations, it's a Versace!"

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Developments

1) Molecular/genetic understanding of hereditary hearing loss vastly enhanced over last 10 years

- Genetic testing and Genetic Evaluation is now an integral part on the assessment of children with hearing impairment

2) Early intervention [medical vs. surgical] now standard of care with limitations

3) Genetic treatment may be the choice in the future

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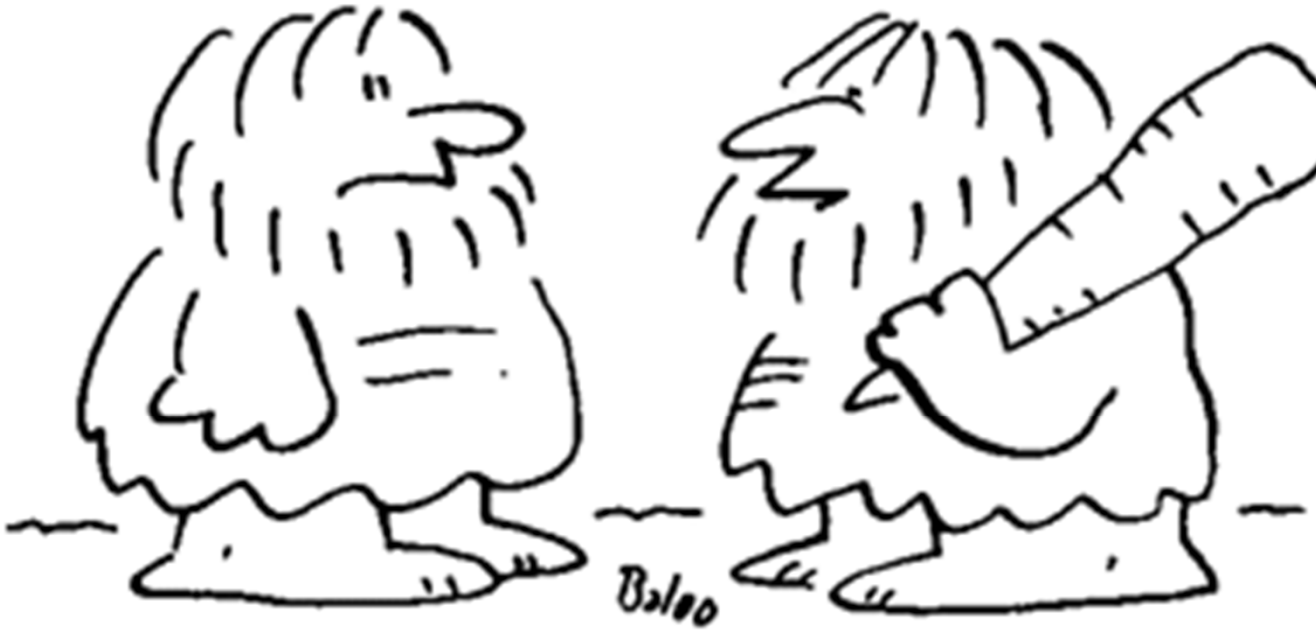

"You look different—have you been evolving or something?"

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Definition of Evolution

"Evolution is a process that results in heritable changes in a population spread over many generations"

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Evolution and Birth Defects

Birth defects are suppose to happen

Birth defects can be advantageous

Birth defects can be deleterious

In search of individuality

Birth defects can be silent

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Mutated miR-96 gene
14 April 2009. Chrissie Giles

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Stage12-4th week of gestation

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Embryology of the ear placode

Images of the lateral view of the human embryonic head from week 5 (stage 14) through to week 8 (stage 23)

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RNA in situ hybridization of Pds in noncochlear regions of the mouse inner ear.

Everett L A et al. PNAS 1999;96:9727-9732

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Mutations in *OTOGL*, Encoding the Inner Ear Protein Otogelin-like, Cause Moderate Sensorineural Hearing Loss
Kemal O. Yariz, et al. AJHG Volume 91, Issue 5, 2 November 2012, Pages 872–882

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Newborn mice lacking the *Slitrk6* gene (right) have severe reductions in the numbers of nerve fiber bundles innervating the inner ear compared to wild-type animals (left).

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The ATP-dependent chromatin remodeling enzyme CHD7 regulates

Cochlea and Kidney a genetic relationship

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Statoacustic ganglion

Otocyst

Basal turn of the cochlea

Tip of digits

Vibrissae

Nasal/Oral epithelia

Amniotic membrane

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Multi-system gene expression: 30,000 genes

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A systems Biology of early mouse inner ear organogenesis: gene expression, patterns, networks and pathways.

Samin Ahmed Sajan, PhD.
University of Washington, May 2008

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An inner ear gene expression database.

Chen ZY, Corey DP Assoc Res Otolaryngol. 2002 Jun;3(2):140-8.

Microarray technology

Mouse cochleas were examined at two developmental stages (P2 and P32) using GeneChip oligonucleotide arrays

> 10,000 genes were found to be expressed in the cochlea

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Gene Function and Hearing

Developmental Time

Gene Expression

Gene Expression Transformation

Gene Regulation

Genetic susceptibility

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Identifying Infants with Hearing Loss

Undetected hearing loss can delay speech and language development

All states and U.S. territories also have established Early Hearing Detection and Intervention (EHDI) programs

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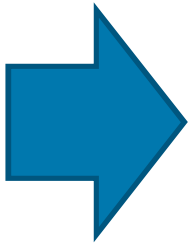

Infant Hearing Loss

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Hearing Loss

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Case 5 - CATSHL

- Camptodactyly
- Tall Stature
- Congenital bone abnormalities
- Congenital hearing loss – diagnosed as isolated non-syndromic at birth (moderate bilateral SNHL)

Toydemir, et al. A Novel Mutation in *FGFR3* Causes Camptodactyly, Tall Stature, and Hearing Loss (CATSHL) Syndrome, *AJHG* 2006; 79, 5

Mutation in *FGFR3* (1862G→A): CATSHL syndrome

CATSHL syndrome

Mutation in the FGFR3 gene

Chromosome 4

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ENT Medical Work UP

ABR testing - moderate CHL right and normal hearing left

CT scan of temporal bones

- bilateral dysplasia of bony labyrinths
- normal cochleae, IACs, vestibular acqueducts, and ossicles
- Possible anomaly of right facial nerve

Testing for Pendred Syndrome - Insurance company rejected testing unless recommended by Medical Genetics

Referral to Genetics

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Medical Genetics Findings

1. Cervical fusion – fusion of C1-C2, retrolisthesis of C3 on C4, C6 and C7 fusion
2. Facial asymmetry
3. Speech/language delay
4. Hand and arm anomalies
5. DX: Klippel Feil Syndrome
6. No Genetic testing needed

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Klippel-Fiel Syndrome

Most Common Associated Abnormalities

Anomaly	Percentage of Patients
Congenital scoliosis	> 50 %
Rib abnormalities (excluding cervical ribs)	33%
Deafness	30%
Genitourinary abnormalities	25-35%
Sprengel's deformity	20-30%
Synkinesia	15-20%
Cervical Ribs	12-15%
Cardiovascular abnormalities	4-29%

Tracy, M.R, Dormans, J.P., and Kusumi, P. *Klippel-Fiel Syndrome,* Clinical Orthopaedics and Related Research, 2004.

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Clinical Application

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Genetic Testing vs. Genetic Evaluation

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Iris Colobomas

Cat-Eye syndrome

Preauricular tags/pits

Stenotic ear canals

22q deletion

Mixed Hearing loss

Robin Sequence

Micrognathia
Cleft palate
Apnea

Stickler Syndrome

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Clefting

Cleft lip/palate

Van Der Wood syndrome

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Genetic Testing:

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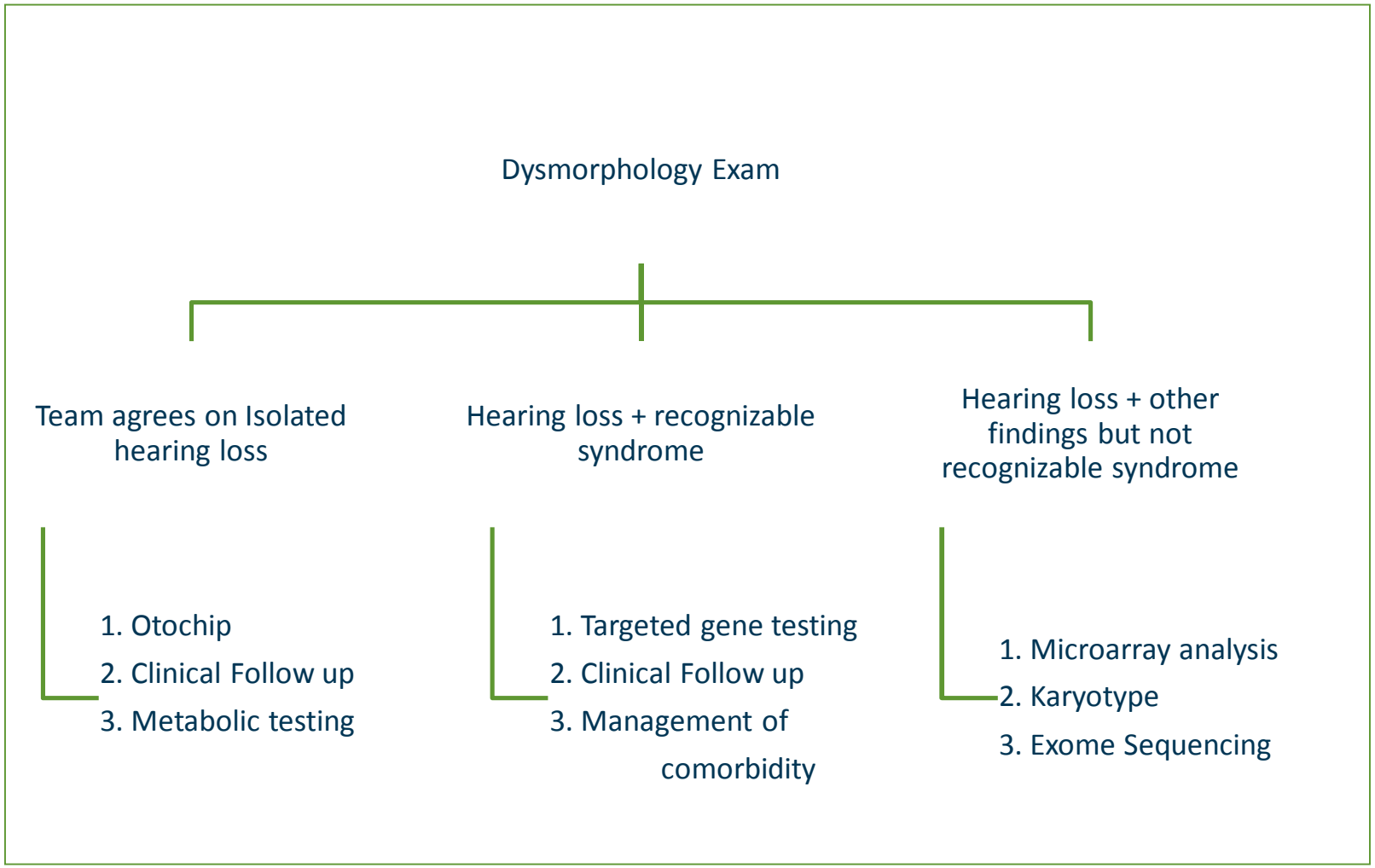
Genetic Evaluation:



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