The New Genetics: Concepts We should know

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Special Needs

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

- 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

- Me
- Family
- Friends
- School
- Community
- Wilder Society

Genetic Inheritance

Environmental Experience

Establishment of a System
Medical Special Needs in the US

*Medical Genetics*

- 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).

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

**Medical Genetics**

- 20-40% of children with hearing loss have other disabilities.
- Genetic conditions have been described to include hearing loss and other special needs.
- Conditions have been described to present with deafness.

**Other Diagnoses Associated with Hearing Loss**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
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<tbody>
<tr>
<td>Learning difficulties</td>
<td>10.7</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>9.8</td>
</tr>
<tr>
<td>Attention difficulties</td>
<td>6.6</td>
</tr>
<tr>
<td>Blindness and low vision</td>
<td>3.9</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3.5</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>1.5</td>
</tr>
<tr>
<td>Other conditions</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Gallaudet Research Institute, 2003
Developments

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

2) Genetic testing now integral for evaluation of hearing impairment in children

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

Definition of Evolution

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

Darwin's Theory of Evolution

- Natural selection working on variation
- Random mutations give rise to changes
- More favorable mutations are passed on to next generation
- Changes get propagated to generate more “competitive” species
Evolution and Birth Defects

- Birth defects are supposed to happen
- Birth defects can be advantageous
- Birth defects can be deleterious
- In search of individuality

Genetic Diversity

Pea Diversity

Human Diversity

Mutated miR-96 gene
14 April 2009. Chrissie Giles

Stage 12-4th week of gestation
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)

From Fish to Mammals

Development of the three ossicle middle ear

Prestin Gene
Changes in the Prestin Gene

Normal expression of Noggin in the developing inner ear

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

Using embryonic tissue at different stages:
More than 5000 genes change expression through inner ear embryogenesis
Identified 983 candidate genes for human deafness

An inner ear gene expression database.
Chen ZI, Carey DP.
Neurology Service, Massachusetts General Hospital, Boston, MA, USA.

• 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
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).

The ATP-dependent chromatin remodeling enzyme CHD7 regulates proneural gene expression and neurogenesis in the inner ear.

Gene Function and Hearing

- Developmental Time
- Gene Expression
- Gene Expression Transformation
- Gene Regulation
- Genetic susceptibility

Significance of Hearing Loss

- Hearing impairment one of the most common sensory deficits in children & significant healthcare problem
- 1 - 2 infants per 1000 births have significant hearing loss
  - Bilateral severe-profound
- Up to 4/1000 births mild-moderate or unilateral HL included (Steel KP Science 1998;279:1870-71)
- ≈ 40,000 infants born/year w/ significant HL
- ≈ 4000 profoundly deaf
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

**Hearing Loss**

**Symptom**
- Additional comorbidity?
- Additional medical risks?
- Genetic predisposition to hearing loss

**Disorder**
- Is isolated hearing loss truly isolated?

Illustrative Cases
Case 1 – 7 month old male
• Born at term, uncomplicated pregnancy, no parental concerns
• Referred newborn hearing screen
• Identified with moderate bilateral SNHL at 6 wks. of age
• Physical exam – unremarkable, no dysmorphology
• ENT medical workup –
  • Testing for Connexin 26 and 30 - negative
  • Diagnosed with isolated hearing loss

Genetics Consultation – 7 months of age
Due to persistent parental concerns a genetic consultation was requested

Branchio-Oto-Renal (BOR) Syndrome
• Autosomal dominant
• Hearing loss – conductive, SN, mixed
• Abnormalities of outer, inner, or middle ear
• Renal problems
• Branchial cysts or tracts along neck muscles

Case 2 – 2 ½ year old Male
• Referred because of unusual appearance. “People ask me about his ethnic background.”
• Parents report normal development except for speech delay
• Parents unsure about newborn hearing screen results
• Audiology/ENT evaluation inconclusive for hearing loss
Genetics Evaluation

- Sedated ABR – sloping mild to moderately severe high frequency SNHL
- Physical Findings: hypertelorism, prominent ears, midface hypoplasia, diastrophia canthorum
- Requested to see other members of the family

Genetics Consult

- Dad reported:
  - Untreated partial hearing loss
  - Early graying
- Dad has similar facial features to proband
- 4 year old sibling with:
  - Similar features and Iris Heterochromia
  - Previously undiagnosed mild/moderate high frequency sensorineural hearing loss
- Genetic testing positive for Waardenburg syndrome in all three members of the family

Waardenburg Syndrome

- Displacement of the inner-canthi
- SNHL - usually profound, UL or BL
- Pigmentary changes
  - Partial albinism, pigment changes, hair, skin and iris
- White forelock or graying by age 30

Case 3 – 2 year old male

- Presented to Pediatric ENT at 2 years of age due to hearing management concerns
- Complicated early history:
  - Born at 35 wks, EGA
  - 2 month NICU stay
  - G-Tube
  - ASD/VSD repair and pacemaker
  - Several hand surgeries
- R ear microtia, heart and limb abnormalities, and torticollis
- Receiving speech, occupational, physical, and developmental therapies
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 aqueducts, and ossicles
  - Possible anomaly of right facial nerve
- Testing for Pendred Syndrome - Insurance company rejected testing unless recommended by Medical Genetics
- Referral to Genetics

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

Klippel-Fiel Syndrome

Most Common Associated Abnormalities

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Percentage of Patients</th>
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<tbody>
<tr>
<td>Congenital scoliosis</td>
<td>&gt; 50 %</td>
</tr>
<tr>
<td>Rib abnormalities (excluding cervical ribs)</td>
<td>33%</td>
</tr>
<tr>
<td>Deafness</td>
<td>30%</td>
</tr>
<tr>
<td>Genitourinary abnormalities</td>
<td>25-35%</td>
</tr>
<tr>
<td>Sprengel’s deformity</td>
<td>20-30%</td>
</tr>
<tr>
<td>Synkinesia</td>
<td>15-20%</td>
</tr>
<tr>
<td>Cervical Ribs</td>
<td>12-15%</td>
</tr>
<tr>
<td>Cardiovascular abnormalities</td>
<td>4-29%</td>
</tr>
</tbody>
</table>


Case 4 – 5 year old male

Referred for a genetic evaluation due to persistent unspecific complaints and progressive hearing loss

Significant History
- Identified with SNHL at 3 years of age
- ENT Medical Work Up
  - Testing for Connexin 26 and 30 – negative
  - Managed as isolated hearing loss, etiology unknown
Parental Concerns

- Irritable from young age
- Persistent reddish raised rash on skin
- Aversion to touch “like he was in pain”
- Never sweats – even when he is extremely warm

Genetics Evaluation Significant Findings

- Mild corneal opacity
- Mild heart enlargement by echocardiography
- Progressive HL
- Enlarged kidneys
- Raynaud’s phenomenon
- Patient complaint of hand pain

Diagnosis - Fabry Disease

GAL gene testing confirmed the diagnosis of FABRY DISEASE

- Enzyme replacement therapy can reduce lipid storage, ease pain, and improve organ function
- Pain can be treated with anticonvulsants
- Patient needs surveillance for renal failure

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
- Mutation in the FGFR3 gene
- Chromosome 4
Genetic susceptibility: "A1555G" mitochondrial mutation

Multi-system gene expression

Cochlea and Kidney a genetic relationship
**EGPF Expression**

- Statoacoustic ganglion
- Basal turn of the cochlea
- Tip of digits
- Nasal/Oral epithelia

**Otocyst**

**Vibrissae**

**Amniotic membrane**

**Clinical Application**

- 5 year old patient with developmental delay and diagnosis of Cerebral Palsy
- 6 month old patient with seizure disorder with possible neonatal injury
- Neonate with severe hypotonia
- 3 year old with speech delay and possible diagnosis of Autism
- Ataxic child with progressive paraplegia

**Hearing Loss**

- EHDI Program
- Congenital
- Late Onset
  - 60% Genetic
  - Structural anomalies
  - Syndromic (40%)
  - Neonatal (60%)
  - Trauma
- Acquired
  - Maternal infection
  - Prematurity
  - Genetic late onset

**Abnormalities of the inner ear**

- (20% of patients with SNHL)

<table>
<thead>
<tr>
<th>Aplasia</th>
<th>Defect</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michel</td>
<td>Agenesis of the petrous portion of the temporal bone</td>
<td>Autosomal Dominant</td>
</tr>
<tr>
<td>Mondini</td>
<td>Deformed cochlea</td>
<td>AD, seen in Pendred Waardenburg, Treacher Collins, and Wildervaank syndromes</td>
</tr>
<tr>
<td>Scheibe</td>
<td>Cochleosaccular dysplasia</td>
<td>Autosoma recessive</td>
</tr>
<tr>
<td>Alexander</td>
<td>Limited cochlear duct differentiation</td>
<td>High frequency hearing loss, AD, AR.</td>
</tr>
<tr>
<td>Enlarged Vestibular Aqueduct</td>
<td>Autosomal dominant and recessive</td>
<td>Pendred syndrome</td>
</tr>
</tbody>
</table>
Iris Colobomas

- Cat-Eye syndrome
- Preauricular tags/pits
- Stenotic ear canals
- 22q deletion
- Mixed Hearing loss

Robin Sequence

- Micrognathia
- Cleft palate
- Apnea

Stickler Syndrome

- Micrognathia
- Hypermobility
- Mixed hearing loss
- Mutation in Collagen gene

Clefting

- Cleft lip/palate

Van Der Wood syndrome
Genetic Testing vs. Genetic Evaluation

1. Medical Genetics Evaluation

2. Genetic Testing
   - Otochip
   - Clinical Follow up
   - Metabolic testing

3. Urine Testing
   - Blood Testing
   - Dysmorphologic Evaluation

Genetic Evaluation:

- Dysmorphology Exam
  - Team agrees on isolated hearing loss
  - Hearing loss + recognizable syndrome
  - Hearing loss + other findings but not recognizable syndrome
  - 1. Otochip
  - 2. Clinical Follow up
  - 3. Metabolic testing
  - 1. Targeted gene testing
  - 2. Clinical Follow up
  - 3. Management of comorbidity
  - 1. Microarray analysis
  - 2. Karyotype
  - 3. Exome Sequencing

Testing:

- Otochip
- Karyotype
- Microarray
- Exome Sequencing
  - 19 genes involved in hearing loss and Usher syndrome
  - Gross Aneuploidies
  - Deletions/Duplications
  - Sequencing of all encoding regions

Questions

Answers