GENETICS OF COMMUNICATION DISORDERS

Communication Disorders
Genetics
- Neurodevelopmental Disabilities
- Congenital anomalies and syndromes
- Hearing and deafness
- Speech disorders

1. Neurodevelopmental Disorders

Genetics of Autism
- Undisputable genetic basis
- Complex inheritance
- Etiologic heterogeneity
- Genetic heterogeneity
- Likely environmental modifiers

Current Climate
- Increasing number of referrals
- New technologies
- Reported associations
- Linked loci
- Reimbursement issues
- Evidenced-based medicine
- Cost-benefit relationships

‘Multifactorial Inheritance’ of Autism
- Recurrence risk (sibs)
  - 7% if affected child is female
  - 4% if affected child is male
  - 33 - 50% after 2 affected
- Relative risk (recurrence)
  - Autism – 22.3
  - Asperger – 13.4
- Sibling risk ratio ($\lambda_s$)
  - 100 – 150
Partial List of Genetic Syndromes with a Reported Association with Autism

<table>
<thead>
<tr>
<th>NO.</th>
<th>SYNDROME/GENE</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fragile X syndrome</td>
<td>Apert syndrome</td>
</tr>
<tr>
<td>2</td>
<td>Rett syndrome</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td>3</td>
<td>Angelman syndrome</td>
<td>De Lange syndrome</td>
</tr>
<tr>
<td>4</td>
<td>Prader-Willi syndrome, Noonan syndrome</td>
<td>Smith-Lemli-Opitz syndrome</td>
</tr>
<tr>
<td>5</td>
<td>Down syndrome</td>
<td>Smith-Magenis syndrome</td>
</tr>
<tr>
<td>6</td>
<td>Neurofibromatosis</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>7</td>
<td>CHARGE syndrome</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>8</td>
<td>Shprintzen syndrome (22q11 deletions)</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>9</td>
<td>Cohen syndrome</td>
<td>Sotos syndrome</td>
</tr>
<tr>
<td>10</td>
<td>PTEN associated disorders</td>
<td>Oculo-auriculo-vertebral spectrum</td>
</tr>
<tr>
<td>11</td>
<td>Hypomelanosis of Ito</td>
<td>Joubert syndrome</td>
</tr>
<tr>
<td>12</td>
<td>Lujan-Fryns syndrome</td>
<td>Myotonic dystrophy, Duchenne dystrophy</td>
</tr>
</tbody>
</table>

Projected Diagnostic Yield of an Extended Evaluation

- **High-resolution chromosome studies**
  - Range (3-5%)
- **aCGH**—beyond what would be detected by chromosomal analysis
  - Range (5-20%)
- **Fragile X**
  - Range 2 - 10%
- **MECP2**
  - 3-13%—women only, total ~ 2.6%
- **PTEN**
  - 3 - 6%—if head circumference >2.5 SDs
- **Other**
  - Metabolic disorders, hearing loss, neurocutaneous syndromes, genetic syndromes, cerebral dysgenesis, teratogens

* Mental Retardation
- Significant sub-average intellectual behavior
  - IQ < 68 (Stanford – Binet)
  - IQ < 70 (Wechsler)
- AND
- Deficits in adaptive behavior

‘Normal’ IQ = 100 $\pm$ 15 (70 – 130)

<table>
<thead>
<tr>
<th>Degree of MR</th>
<th>IQ equivalent</th>
<th>Z score (-SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline</td>
<td>70 – 78</td>
<td>1.25</td>
</tr>
<tr>
<td>Mild</td>
<td>55 - 69</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>40 – 54</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>25 – 39</td>
<td>4</td>
</tr>
<tr>
<td>Profound</td>
<td>&lt; 25</td>
<td>5</td>
</tr>
</tbody>
</table>

Polygenic Inheritance
- IQ displays all of the traits of polygenic inheritance
- Distributed in a normative manner
- Close relationship to parental IQ’s
- Quantitative trait
- No sexual dimorphism
- By definition, 2.5% of the general population has an IQ in the MR range

Identifiable Causes of Mental Retardation

- **Chromosome abnormalities** 25-30%
- **Recognizable syndromes** 3- 7%
- **Known single gene disorders** 3- 9%
- **Structural CNS abnormalities** 7-17%
- **Prematurity complications** 2-10%
- **Environmental/teratogenic** 5-13%
- **“Cultural-familial”** 3-12%
- **Metabolic/endocrine causes** 1- 5%
- **UNKNOWN** 30-50%
Cerebral Palsy
Definitions (My favorite)

- A clinical set of static encephalopathies linked by their expression of variable disabilities of movement / posture

Cerebral Palsy
Epidemiology

- Uncommon, prevalence 2/1000 at time on entry into school
  - 86/1000 in extreme prematurity
  - 1.2/1000 in term infants
- Incidence stable
  - Has not decreased in decades despite improvements in prenatal / perinatal care

Cerebral Palsy
Etiology

- Premature infants
  - Can identify etiology ~75%
    - 10% prenatal
    - 60% perinatal / neonatal
    - 30% not clear
- Term infants
  - Can identify etiology ~80%
    - 50% prenatal
    - 35% perinatal / neonatal
    - 15% not clear

Cerebral Palsy
Possible causes

- Hypoxic - ischemic encephalopathy
- Genetic syndromes
- Chromosome anomalies
- MCA without unifying diagnosis
- Cerebral dysgenesis
- Teratogenic
- Metabolic disorders
- Coagulopathies
- Trauma
- Slowly progressive neuromotor disorders

Diagnostic Yields

<table>
<thead>
<tr>
<th></th>
<th>1970’s</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single anomalies MCA / syndromes</td>
<td>20%</td>
<td>25-30%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>30-50%</td>
</tr>
<tr>
<td>Mild Mental Retardation Severe mental Retardation</td>
<td>10-15%</td>
<td>40-50%</td>
</tr>
<tr>
<td></td>
<td>50-60%</td>
<td>80% +</td>
</tr>
<tr>
<td>Autism</td>
<td>6-8%</td>
<td>35-45%</td>
</tr>
</tbody>
</table>

2. Congenital Anomalies and Syndromes
Orofacial Clefts

Cleft Lip and Palate
- Second most common structural congenital anomaly
  - 1 / 1000 live births
- Can occur as isolated malformation or in the context of multiple anomalies

Etiology

Cleft Lip / Palate

- Without other anomalies: 50 - 55%
  - "isolated" "non-syndromic"
- With other anomalies: 45 - 50%
  - Slightly more common with CP

Communication Issues in Orofacial Clefts

- Palatal dysfunction
- Oromotor problems
- Feeding and swallowing difficulties
- Incidence of LD 3X increased
- Otitis media / hearing

(Pierre) Robin Sequence
- Sequence of events secondary to primary anomaly (mandibular hypoplasia)
- May occur alone or in the context of a syndrome
- Neonatal emergency if airway compromise

Genetic Syndromes
- Hundreds of described genetic syndromes
- Most have associated neuro-developmental problems
- Most have speech and language disorders
  - Described by geneticists and thus often poorly characterized by SLP standards
Common Syndromes for the SLP

- Chromosome abnormalities
  - Down syndrome (47 +21)
  - Turner syndrome (45 –X)
  - 22q deletion spectrum (del 22q11)

- Fragile X syndrome
- Fetal alcohol syndrome
- Stickler syndrome
- Williams syndrome
- Prader –Willi syndrome
- Noonan syndrome
- Neurofibromatosis

Sotos Syndrome

- Original Description of Sotos Syndrome
  - Five cases from Sotos et al 1964 with four key features
    - Overgrowth
    - Advanced bone age
    - Developmental delay
    - Characteristic facial appearance

- Hypotonia
  - Almost a universal feature in Sotos Syndrome
  - Low muscle tone, not weakness
  - Concept of fighting gravity
  - AFO’s are oftentimes helpful in early stages of walking
  - Treating hypotonia is not disease specific
    - i.e. your child’s therapist doesn’t have to be familiar with Sotos Syndrome to help

- Since the description of Sotos Syndrome in 1964, literally hundreds of cases have been identified
- New cases are not considered ‘reportable’
- Affects all racial and ethnic groups
- Estimated incidence 1:5,000 to 1:15,000
**Developmental Delay**

- Some form of learning difference is present in 97% of individuals with NSD1 mutations
- In general developmental progress is linear
- Reported IQ range 20 – 120
- Poor coordination / fine motor control
- Early developmental ‘scores’ have little predictive value

**A unique feature of Sotos syndrome lies in the “natural history” of this condition. In contrast to most other conditions with neuromotor impairments, the early developmental delays seen in patients with Sotos syndrome are poorly correlated with long term outcomes.**

*example: things often get better*

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**Behavioral Changes**

- Attention deficit (hyperactivity) disorder
- Phobias
- Obsessions / compulsions
- Impulsivity
- Tantrums
- Frustration behaviors

**Behavioral Changes**

- Social naivety
- More confident with younger children and adults than peers

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**Socialization and Communication**

- Autism
- Autistic behaviors
- PDD nos
- None of the above

**Speech and Language**

- Expressive language impairments
  - Reduced variety of words
  - Shorter sentences
  - Simplified grammar
- Sound production impairments
  - Create their own linguistic ‘rules’

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Speech and Language

- Voice differences
  - Hoarseness, hypernasal, pitch changes
- Social-pragmatic differences
  - Monotone speech
- Stuttering
  - Later onset than typical (even into adolescence)

3. Hearing Loss

Etiology of Congenital Deafness

- Recessive: 42%
- Dominant: 12%
- X-linked: 4%
- Other genetic: 2%
- Non-genetic: 40%

Congenital Cytomegalovirus

- CNS changes
  - Microcephaly
  - Intracranial calcifications
  - Mental retardation
  - Cerebral palsy
  - Optic atrophy, retinopathy, cataracts, microphthalmia
  - Neurosensory hearing loss
    - May be the only manifestation

- Primary infection occurs in 2.4% of pregnancies
- Virus crosses placenta 30–40% of the time
- About 1% (range 0.5–2.5%) of infants congenitally infected with CMV
- Hearing loss occurs in 8–12% of those prenatally infected
- Therefore, 0.05–0.2% of all newborns are predicted to have CMV-related hearing loss
- In the US, about 5000 newborns per year have CMV-related hearing loss
- (May be the most common identifiable cause)

Fetal Alcohol Spectrum Disorders

- How common are they?
  - Alcohol-related birth defects are the most common cause of MR, LD, SLD
  - An estimated 1/3 of all neurodevelopmental disabilities could be prevented by eliminating alcohol exposures

Fetal Alcohol Syndrome

- Limb abnormalities
- Crease differences
- Cardiac
- Small genitalia
- Ocular
- Skeletal
- Auditory
  - (25–30% of children with FAS have NSHL)
  - Overall incidence of newborn hearing loss secondary to FASDs unknown)
Non-Syndromic, Monogenic Heritable Hearing Loss

- DFN = deafness
  - A= dominant (64 loci)*
  - B= recessive (98 loci)*
  - ( ) or X = X-linked (8 loci)
  - (e.g. DFNB1 = recessive hearing loss gene #1)
- Over 750 ‘associated genes’

* OMIM search 2013 : Non-syndromic Hearing Loss DFNA64
Non-syndromic Hearing Loss DFNB8

Connexin 26 (DFNB1 / GJB2)

- Phenotype
  - non-syndromic
  - normal vision and vestibular function
  - non-progressive (2/3)
  - hearing loss = mild to profound with intra- and inter-familial variability
  - few kindreds are progressive and asymmetric
- Gene mapped to 13q12
  - 2 common mutations = 10% all pre-lingual deafness:
    - 35delG (85% N. Europeans)
    - 167delT (Jewish)
  - 1 allele causes dominant deafness (DFNA3)

Testing for the Etiology of Newborn Hearing Loss

- Potentially 25% are congenital CMV or Connexin 26 related

Examples of Single Genes as Causes of Hearing Loss

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFNA1</td>
<td>DFNA1</td>
<td>Regulation of actin polymerization in hair cells of the inner ear</td>
<td>Abnormal actin polymerization of hair cells of the inner ear</td>
</tr>
<tr>
<td>DFNB1</td>
<td>Connexin 26/GJB2</td>
<td>Facilitated rapid ion transport by-passing membrane diffusion</td>
<td>Disrupted ion transport</td>
</tr>
<tr>
<td>DFNB2</td>
<td>MYO7A</td>
<td>An unconventional myosin expressed only in the Organ of Corti. Bridges the steroctilia to the extracellular matrix</td>
<td>Abnormal anchoring of cilia</td>
</tr>
<tr>
<td>DFNB2</td>
<td>DFNB2</td>
<td>(X-linked perilymphatic gusher with fixed stapes)</td>
<td>Regulation of mesenchymal fibrocytes</td>
</tr>
<tr>
<td>DFNA2</td>
<td>POU3F4</td>
<td>Transcription factor</td>
<td></td>
</tr>
</tbody>
</table>

Hearing Loss Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gene function</th>
<th>Hearing loss features</th>
<th>Major non-hearing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alport syndrome</td>
<td>Collagens 4A3, 4A4 or 4A5</td>
<td>Basement membrane protein</td>
<td>Bilateral, sensorineural, high frequency, childhood onset, progressive</td>
<td>Nephritis with kidney failure</td>
</tr>
<tr>
<td>Branchio-oto-renal syndrome</td>
<td>TSLC1</td>
<td>Regulation of genes coding for growth and development of embryo</td>
<td>Bilateral sensorineural, conductive or mixed. Often asymmetric. Mild to profound</td>
<td>Abnormal development of ears, kidneys and branchial arch derivatives</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen syndrome</td>
<td>KCNJ1, KCNE1</td>
<td>Potassium channel</td>
<td>Congenital, bilateral sensorineural</td>
<td>Cardiac conduction problems (long QT). May have fainting spells or sudden death</td>
</tr>
</tbody>
</table>

Jervell and Lange-Nielsen Syndrome

- AR
- Profound congenital deafness
- Syncopal attacks / sudden death due to prolonged QT
- High prevalence in Norway
Jervell and Lange-Nielsen Syndrome

- Mutations are in one of two genes that co-assemble in a potassium channel (KCNQ1, KCNE1).
- Disrupts endolymph production in the stria vascularis.
- Alleles in KCNQ1 produce isolated long QT syndrome.
  - AD or AR
  - (3 other genes may also produce long QT)

Hearing Loss Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gene function</th>
<th>Hearing loss features</th>
<th>Major non-hearing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2 (merlin)</td>
<td>Inhibits cell-cell communication and proliferation</td>
<td>Sensorineural hearing loss due to vestibular schwannomas</td>
<td>Neurological tumours (meningiomas, retinal hamartomas, gliomas)</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>SLC26A4</td>
<td>Specific transporter of iodine</td>
<td>Sensorineural hearing loss</td>
<td>Bilateral sensorineural deafness due to defect in sodium-fluxing</td>
</tr>
</tbody>
</table>

Medical Genetic Evaluation of Hearing Loss

Stage 1
- Medical Genetics
- Audiology
- Otolaryngology

Stage 2
- Vestibular
- Ophthalmology
- CT of temporal bones
- Urinalysis/serum creatinine
- Serology

Stage 3
- Perchlorate discharge (if CT abnormal)
- Electrocardiogram
- Electroretinogram
- DNA

4. Speech-Language Disorders

Speech-Language Disorders

- Dysfluencies
- Articulation disorders
- Abnormalities of voice
- Language impairments

Genetics of (Developmental) Apraxia

- Syndromes
  - 22q deletions
  - Galactosemia
  - Assorted CNVs
- Children with DAS often have family members who have a history of communication disorders or learning disabilities
Definitions of Reading Disability (Dyslexia)

- Significant difficulty learning to read and spell despite adequate intelligence and opportunity, and without demonstrable neurological, sensory, or emotional handicap

Qualitative Phenotype
- Positive history of reading and spelling problems
- P or V IQ > 90
- Reading Quotient < 0.80
- Ratio of reading/spelling scores to expected ability based on age and intelligence

Quantitative Phenotype
- Discriminant score based on a function developed through the testing of 125 disabled readers and 125 normal readers on a battery of achievement tests

Types of Dyslexia

- Surface: person can read words phonetically but has problems with whole word recognition (i.e. yacht --> yatchet).
- Phonological: person can read familiar words by using whole word method but has difficulty "sounding out" words that are new or letter-to-sound decoding problems.
- Spelling: person can read individual letters that lead to reading words if given enough time but has problems recognizing the word as a whole and phonetically (i.e. men --> h-e-n).
- Direct: person can read aloud without comprehension that is similar to speech comprehension aphasias like anomia.

Gene Identification: Positional Cloning Strategy

- Genetic map
- Physical map
- Candidate genes
- Linkage
- Association
- Mutation analysis
- Verify in independent population

What might dyslexia genes be doing?

- Affecting specific cell type
  - magna (rapid transmitting) v parvo cells
- Affect myelin in some way

Dyslexia Genes

- DCDC2 gene
  - Gene map locus 6p22.1
  - encodes a protein containing 2 doublecortin peptide domains
  - Doublecortin gene (DCX) – produces X-linked lissencephaly

DCDC2

- A deletion in a putative regulatory sequence in DCDC2 is present in ~20% of persons with dyslexia.
- Over 20 variations (alleles) of this regulatory (enhancer) sequence have been identified
- Knockout mouse: Complete silencing of the gene
  - Neuronal migration disorder ~ lissencephaly
DCDC2

- RNAi: slowing down the gene

Results in dyslexic mouse!