The Clinical Genetic Approach to Intellectual Disability and Autism
An Introduction

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Learning Objectives

- Describe what geneticists do.
- Learn about components of a genetics evaluation for patients with ID/Autism.
- Understand how this benefits patients and families?
- Know when and where to refer to genetics.
What I will not cover

- Clinical diagnosis of ID or ASDs.
- Management/treatment of genetic conditions.
- Research into ID/ASD.
Genetic  Environmental

- Downs syndrome
- Phenylketonuria (PKU)
- Hemophilia
- Club foot
- Peptic ulcer
- Diabetes
- Heart disease
- Tuberculosis
- Scurvy
**Genetics** is the study of heredity and seeks to explain the basis of individual variation.

**Medical Genetics** is the field of medicine that deals with genetically influenced biologic variation relevant to human health and disease.
Clinical Genetics is increasingly relevant for the adult population

Angelina Jolie
BRCA 1/2 genetic testing

Hank Gathers
Hypertrophic cardiomyopathy

Jay Monaghan
Colon cancer
Terms and definitions

- **Gene**: unit of inheritance
- **Genome**: an individual’s entire complement of DNA
- **Exome**: coding sequence of all genes, ~ 2% of the genome
- **Alleles**: alternate versions of a gene
- **Dominant**: mutation in 1 copy is sufficient to cause condition.
- **De novo**: mutation started in patient, not inherited.
- **Recessive**: mutation in both copies required to cause condition.
- **X-linked**: disease gene on the X-chromosome, implies maternal inheritance, and differential effects on males and females.
- **Mitochondrial**: DNA encoded by mitochondria are derived from egg
- **Consanguinity**: “with blood” marriage between relatives.
- **Incomplete penetrance**: having a gene mutation but not expressing the condition.
The Road to Being a Geneticist
3-8+ years of training after MD or MD PhD

Medical School

Internship and Residency
(1 to 3 years)

Genetics Residency & Fellowship
(2 to 5 years)

Board Certification

and recertification....
How is Clinical Genetics different from other medical specialties?

- Not defined by *organ system* (eye, heart, kidney. (The organ of interest is the genome).
- Not defined by *age*. (Genetic conditions occur at every age).
- Genetic testing can *predict* future disease, and has immediate implications for *family* members.
Medical Genetics combines very old and very advanced methods

<table>
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<tr>
<th>History</th>
<th>MRI</th>
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<tbody>
<tr>
<td>Physical Exam</td>
<td>Molecular testing</td>
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<tr>
<td>Family history</td>
<td>Array CGH</td>
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<tr>
<td>X rays</td>
<td>Whole exome sequencing</td>
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Benefits of Genetics Diagnosis

- For the family:
  What is the cause? How did this happen? What can we expect?
  Will it happen in future children? Can we test for it in a future pregnancy?
  Are other family members at risk?
  What support resources are available?
Benefits for providers

- End diagnostic odyssey
- Clarify etiology, prognosis, treatment options, and recurrence.
- Research/treatment protocols.
What about treatment for genetic diseases?

Learn About KALYDECO™ (ivacaftor) and the G551D-CFTR* Protein Defect

First FDA approved genetic based treatment for cystic fibrosis.
What types of patients do clinical geneticists see?

- Prenatal genetics
- Pediatric genetics
- Neurodevelopmental disorders
- Biochemical genetic disorders
- Cancer genetics
- Adult genetics
- Healthy patients at risk.
- Pharmacogenetics.

Increasing Developmental Concern

9 month
18 month
24/30 month

Administer Screening Tool

Positive

Refer for Developmental and Medical eval
And Early Intervention

Normal

Schedule Return visit

Positive

DSM
ADOS
ADI

Developmental disorder Diagnosed?

No

Special Needs Child

Adapted from Pediatrics v 118:405-20
“Families of children with DD/MR expect and deserve to know, whenever possible, the underlying etiology of their child’s diagnosis. Pediatricians often refer such patients to consultants, including clinical geneticists, to assist with diagnosis and management....”
FIGURE 1
Diagnostic process and care planning. Metabolic test 1: blood homocysteine, acylcarnitine profile, genetic testing.
Genetics is relevant to neurodevelopmental disorders.

- **Global developmental delay**: In children < age 5 y, -2 SD in 2 or more domains: motor, language, social, cognitive, ADLs.
- **Intellectual disability**: disorder of cognition and adaptive function with onset prior to age 18. Diagnosis made more reliably after age 5y. Prevalence: 2.5% of population.
Autistic spectrum disorder
Core Features include abnormalities of:

- Social interaction
- Language and imaginative play
- Limited range of interests and activities
Who is affected by autism?

- Prevalence of 1:68 children (CDC)
- Affects all races and ethnic groups
- Symptoms before 18 months
- 4:1 ratio of boys:girls with autism

- Autism is a *spectrum* disorder from mild to severe, and improvement in some over time.
Possible “Red flags” for Autism

**Does not:**
- babble by 12 months
- point/wave by 12 months
- respond to his/her name
- smile in response to smile
- know how to play with toys
- Pretend or play make-believe after age 2

**Has poor eye contact**
- Not interested in other children
- Seems to be in his/her own world
- Violent tantrums
- Lines up objects
- Overly attached to objects
Evidence for a Genetic Etiology of Autism

- 60%-96% concordance in MZ twins*
- 0%-24% concordance in DZ twins*
- Sibling recurrence risk >> population risk (1 in 5)
- Heritability of 90%
- *California Twin study 2011 concordance
  Male MZ twins: 0.58 (strict) 0.77 (broad)
  Male DZ twins: 0.21 (strict) 0.31 (broad)
  “Moderate genetic heritability and substantial shared twin environmental component”
Classification of cause of ID/ASD

- **Timing:** Prenatal, perinatal, postnatal, undetermined.
- **Genetic**
- **Acquired**

- Chromosomal
- XLID
- CNVs
- Metabolic
- Recessive
- Imprinting
- Mitochondrial

TORCH Infections
Fetal alcohol syndrome
Valproate
Hemorrhage
Hypothyroidism

Half of all genes are expressed in the brain!
Epilepsy

Intellectual Disability

Autism

16p11.2 del Fragile X

Rett syndrome

Tuberous sclerosis

NRXN1

Autism

Epilepsy

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NRXN1

16p11.2 del Fragile X

Rett syndrome

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Clinical genetic approach to child with ID or autism

History and Examination
- Birth history
- Teratogens
- Growth
- Medical history
- Family history

ID or Autism as part of syndrome

Teratogens: Alcohol, CMV, Valproate, Rubella
Chromosomal: 47, XYY
CNVs: dup 15q11, dup 17p11, del 22q11.2, del 22q13

ID/ASD alone in an otherwise normal appearing child

Metabolic disorders:

Syndromes:
Approach to the clinical genetics evaluation for DD/MR.
Genetic testing:

- G banding [> 4 Mb]
- FISH [40 to 250 kb per clone]
- BAC array [>150 kb]
- Oligo Array CGH [35kb]
- MLPA [1-10 bp]
- DNA sequence [1 bp]

Slide courtesy of David Miller, MD PhD
ID or autism as part of a recognizable genetic syndrome

- Fragile X syndrome
- Rett syndrome
- Angelman syndrome
- Tuberous sclerosis
- CHARGE
- Smith-Magenis syndrome
- Prader-Willi syndrome
- Sotos syndrome
- PTEN associated hamartoma syndrome
40 yr woman

Head circumference
53.25cm (3-10%)

Hx of developmental delay:
- Intellectual disability
- Non-verbal

Hx of epilepsy

Flattening of the back of the head

Dysmorphic facial features

Uplifted arms

Hx of falling forward, but lately falling backward ("like a tree")
Tests requested

- Whole genome chromosomal microarray
- PWS/AS methylation studies
Lab results

Whole genome chromosomal microarray

arr 15q11.2q13.1(22,770,421-28,981,826)x1

Interpretation: Type I deletion of either Prader-Willi or Angelman Syndrome.
# Angelman Syndrome

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Frequency(%)</th>
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<tbody>
<tr>
<td>Deletion in AS/PWS region (5-7 Mb)</td>
<td>~68</td>
</tr>
<tr>
<td>UPD</td>
<td>~7</td>
</tr>
<tr>
<td>Imprinting center deletion (6-200kb)</td>
<td>~3</td>
</tr>
<tr>
<td>UBE3A mutation</td>
<td>~11</td>
</tr>
<tr>
<td>UBE3A deletion</td>
<td>Rare</td>
</tr>
</tbody>
</table>

![Diagram of Angelman Syndrome genes and regions](image-url)

- Class I (~40% of deletions)
- Class II (~50% of deletions)

IC: Imprinting Center

- ~6 Mb

• Gene Review
Angelman Syndrome

• Gene Review
• J Med Genet 2003;40:87-95
Angelman Syndrome

Genetic Mechanism

- Normal
- Deletion
- UPD
- Imprinting Defect
- UBE3A Mutation

http://www.angelman.org
Family’s response to diagnosis

- The clouds opened and the sunlight appeared.
- Went to Angelman Family Foundation and ordered 2 videos.
- Becoming engaged in raising awareness.
- Why didn’t any of 9 neurologists refer her to genetics.
4 y and 10 month old boy with delay

- Born in Florida at 40 wks to 21 yo mother.
- Emergency C-section. Meconium swallowed, hydrocephalus noted.
- Shunted at 2 days of age. Home at 8 days.
- Delayed. Poor head control. Few words, signs, rolled at 4 years.
- One sz in infancy. G tube placed.
- Moved to MA 2 ½ yr later.
- Previous dx: hydrocephalus (shunted), FTT, cerebral palsy, GER, Global delay
- Seen here by: Neurosurg, GI, Ortho, Neurology
- No prior genetic evaluation or testing.
African-American

Died at 30 y Complications from hydrocephalus
Physical Exam

- Ht, Wt and OFC <3\textsuperscript{rd} centile
- R shunt
- Ears posteriorly rotated
- Pectus excavatum and G tube
- Adducted thumbs and STC
- Spastic quadriplegia, ankle clonus and Babinski sign
• Karyotype  46, XY
• L1CAM:  P333R
• Dx: X-linked hydrocephalus with stenosis of the acqueduct of Sylvius: HSAS
• Hydrocephalus
• Spasticity
• Adducted thumbs
• Mental retardation
African-American

Died at 30 y Complications from hydrocephalus
Girl with a new diagnosis

- 2 y 7 month old with failure to thrive, and delay
- 31 yo mother, BW 5 lb 7 oz at 42 wks. Breathing issues, temperature issues, feeding. Observed X 1 week. DC to home.
- Wt fell off curve
- Saw Endocrine: w/u negative.
- Saw GI: constipation. ?milk protein intolerance, change to Nutramigen.
- 11 yo healthy sister. Irish/English X Dominican
- Speech delay: hearing normal.
- Ht: 8\textsuperscript{th} centile  Wt.<5\textsuperscript{th}. Head circ. 46.5 (3-10\textsuperscript{th})
There was a 3.5 megabase duplication at chromosome 17p11.2.

VUS 497 Kb dup. at chromosome 7q32.3

37 kb deletion Xq21.33 DIAPH2 gene associated with POF disrupted by translocation.

Which are incidental and which are meaningful?
Potocki-Lupski syndrome (PLS)

- 3.5 MB duplication of 17p11.2
- Clinical features: Poor feeding, GER, FTT, hypotonia, autism, devel delay, sleep apnea, cardiac anomalies.
(1) aCGH testing is recommended as a first-line test for postnatal evaluation of:
   A. Multiple anomalies   B. DD/ID   C. ASD
(2) Further determination of the use of aCGH for evaluation of growth retardation, speech delay and other indications is recommended by prospective studies etc.
(3) Appropriate follow-up for chromosome imbalance identified by CMA is recommended including parental evaluation and clinical genetic evaluation and counseling.
PCP

Organ specific specialist

Genetics
Fragile X syndrome
- mod to severe intellectual disability
- long face
- large ears
- hyperactivity
- autistic behavior
- macroorchidism

Fragile X Premutation Carriers
- premature ovarian failure
- FXTAS (fragile X associated tremor and ataxia syndrome) in men after age 50
- normal prior to that.
Geneticists take care of the family, not just the patient.
How much training do non-genetics physicians have to provide genetics services?

- 2004 survey of US and Canadian Medical schools:
  - 18% < 20 hours; 62% 20-40 hours
  - Predominantly in the preclinical years.
Genetic Testing is not “just a blood test”

- Complex interpretation.
- Complicated forms.
- Does my insurance cover this?
- Which test to order?
- Who is the best person to test?
- Written informed consent documents required by lab and by law.
- Genetic testing is more like surgery or an invasive procedure than a blood test.
What is the solution?

PCPs and specialists learn more about genetics.

Make friends with a geneticist. Learn when to refer to Genetics.
Geneticists improve care of patients with genetics conditions

- Better recognition of genetic conditions
- Greater knowledge of genetic testing
- Always consider implications for family.
Medical Genetics AND Genomics:
a rapidly changing field
Next Gen Sequencing is Here

Cost per Genome

Moore's Law

National Human Genome Research Institute

genome.gov/sequencingcosts
Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability

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ABSTRACT
de Ligt et al.  
Exome sequencing in 100 patients with severe ID (IQ< 50) with prior, negative, extensive genetic testing.  
Identified cause in 16%.  
“We should proceed with optimism and careful thought.. with these new, powerful and yet imperfect tools.”
Autism/ID: Referral to Clinical Genetics

- Dysmorphic features
- Nondysmorphic but multiple medical problems
- Genetic evaluation > 5 years ago
- Positive Family history
- Parental request (is it genetic, what is the chance of next child being affected?)
- Prior to enrollment in research studies
- For whole exome sequencing.
Acknowledgments
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Thank you!
Any questions?