Environmental and Genomic Factors in Neurodevelopmental Disabilities
American Academy for Cerebral Palsy and Developmental Medicine
71st Annual meeting
Montreal, Quebec, Canada
September 13, 2017

**SPEAKER**  
**TOPIC**

**Morning**

7:30  
Hoon (moderator)  
Welcome and Introduction for the Morning

7:40  
Desai  
Genetics 101

8:20  
Bjornsson  
Principles of Epigenetics

9:00  
Fatemi  
Genetic Masqueraders of Cerebral Palsy

9:30-  
Questions and Discussion

9:50-  
Coffee and Tea Break

10:10-  
Leppert  
Developmental Origins of Health and Disease

10:50-  
Levey  
Teratogens

11:30  
Gwynn  
Infantile Epileptic Encephalopathy

11:50-  
Hoon  
Announcements

12:00-  
Lunch– Presentations

Hall  
How Arthrogryposis and Cerebral Palsy have to adjust to the new genetics and epigenetics

**Afternoon**

12:55  
Stashinko (Moderator)  
Welcome and Introduction for the Afternoon

1:00  
Graham  
High Risk Obstetrics- management tests/technologies

1:40  
Gordon-Lipkin  
Prenatal Infections

2:20  
Wilms-Floet  
Adverse Childhood Experiences and Toxic Stress

3:00  
Coffee and Tea

3:20  
Fatemi  
Overview of Gene Therapy Strategies for Neurogenetic Disorders

4:00  
Johnston  
Integrating Knowledge into Clinical Practice

4:40  
Panel Discussion: Clinicians  
International Group from AACPDM

5:20-5:30  
Levey  
Closing Remarks
Learning Objectives

• To understand the types of genetic tests available currently
• To understand why genetic testing is useful and what information should be conveyed to families before sending testing
• To understand how to interpret results and variants

The diagnostic odyssey...is it worth it?

• Why do families opt for genetic testing? Why is getting a genetic diagnosis important?
  – Potential changes in management
  – Recurrence risk information
  – Better idea of prognosis
  – Access to services
  – Psychosocial factors
  • Closure
  • Opportunity to connect with other families
  • Alleviation of guilt/blame

What types of testing are available?

• The old gold standards
  – Karyotype
  – FISH
• Current guideline recommended first tier:
  – Microarray
  – Fragile X testing
• Second tier
  – Panel testing vs.
  – Whole exome sequencing

Chromosomal microarray

• Chromosomal microarray is considered first tier testing for children neurodevelopmental disabilities
• Copy number variations are found in approximately 12-15% of this population

What should parents know about the microarray?

• Possible results
  – Potential need for parental samples
• Possibility of identifying
  – Consanguinity
  – Incidental findings
  – Careers
  – Carrier status
• Insurance cost
  – Commercial insurance process
  – Medicaid process
Possible results
- Positive
- Variant of uncertain significance
- Negative
- Off target
  - Consanguinity
  - Carrier status
- Medically relevant CNVs unrelated to indication

Positive
- Known chromosomal deletion and duplication syndrome often have many resources you can give families
  - Rarechromo.org
  - Simons VIP connect
  - Facebook groups
  - Clinicaltrials.gov

Negative
- If the child warrants further workup
  - Panels
  - Whole exome sequencing

Variants of uncertain significance
- Lab classification
  - Still need to do our homework
  - Is it a deletion or duplication?
  - Partial or full
  - Determine what genes are in the deleted or duplicated region
  - http://firefly.ccs.miami.edu/cgi-bin/ROH/ROH_analysis_tool.cgi
  - Do these genes have any implication in neurodevelopment?
  - Are there any reports of point mutations in those genes causing a neurodevelopmental phenotype?
  - Loss of function tolerated?

How do we interpret a VUS?
- Parental testing always an option, not always useful
- When is parental testing not useful?
  - Few genes in region
  - Recessive conditions
  - Not implicated in neurodevelopment
  - Outcome won’t change approach to patient
- Many labs will do parental testing for variants free of charge-check with the lab

Clinical correlation
- The variant is inherited
  - Parent neurotypical, no incomplete penetrance/variable expressivity likely benign
- The variant is de novo
  - Genes implicated in neurodevelopment likely pathogenic
  - Unknown genes no implication in neurodevelopment still VUS
- Emphasize classification as VUS vs. our interpretation

Example
- 5 year old boy with severe language delays, mild motor delays, and moderate intellectual disability
- Chromosomal microarray sent and revealed a variant of uncertain significance
- Referred to genetic counseling

Result
Partial duplication of DCDC5 is the function of the gene disrupted?
Suggestive for involvement in neuronal migration, learning, memory, and cognition.
Parents are neurotypical per report.
Parental testing pursued

• Maternally inherited
• Our interpretation-likely benign familial variant
• Warranted further testing
• Further testing-revealed a maternally inherited likely pathogenic variant in CDH15
  — Pathogenic mutations cause intellectual disability
  — Incomplete penetrance

Follow up is critical

• When a variant of uncertain significance is found, it is critical to follow research
• Every time you see the patient in clinic, re-do the literature review and research
• Variants can be reclassified to pathogenic or benign as new information becomes available

Where do we go when first tier testing is negative?

• Panels
• Whole exome sequencing
• Should ideally be seen by a GC for counseling beyond first tier

Panels

• Why use panels instead of going to an exome?
  — Specific phenotype
  — Brain malformations
  — Microcephaly
  — Severe epilepsy
  — Ataxia
  — Most will include deletion/duplication testing
  — Complete coverage of all genes
• Disadvantages
  — Proband only-increases risk for variants

Whole exome sequencing

• All first tier testing is negative, but you still suspect and underlying genetic etiology
  — Phenotype not consistent with a specific disorder, or group of disorders or panel done and negative
• Positive in approximately 40% of patients (KK1)

The exome

The majority of disease causing variants are in the exome

What should a family know before sending exome?

• Possible results
• Possible inheritance patterns
• ACMG incidental findings
  — GINA
• Other incidentals
  — Non-paternity
  — Non-maternity

Possible results

• Positive
  — A known syndrome
• Variant of uncertain significance
  — A variant in a known gene that has not previously been reported as pathogenic
  — Variant in a candidate gene
• Negative
  — No changes beyond normal variation
**Positive**
- Known diagnosis
  - Management changes
  - Resources for families
  - Updated counseling on recurrence risk
  - Options for prenatal testing
  - Referrals
  - Screening
- Psychosocial benefits

**Negative**
- Why would exome be negative if we are confident there is an underlying genetic disorder?
  - Intronic changes
  - Deletions/duplications
  - Genes with unknown function

**Variants of uncertain significance**
- Two types of variants
  - Variants of unknown significance in known genes
  - Variants of unknown significance in unknown genes (candidate genes)
- The majority of the time the patient’s mutation has not previously been reported

**Variant of uncertain significance in known gene**
- Most labs follow ACMG guidelines
- However, we still need to do our homework
  - In silico analysis
  - Functional domain analysis
- We know the patient better than the lab does, clinical correlation makes a large difference!!
- But...it’s a lot more complicated than that....

**Variant of uncertain significance in a gene of unknown significance**
- 13 year old girl with obesity, intellectual disability, history of global delays, polycystic ovarian syndrome and abnormal endocrine workup, and dysmorphic features
  - SNP array revealed paternally inherited duplication on 5q23.3
  - Exome pursued

**Example**
- Gene associated with
  - Insulin signal modulator in pancreatic beta cells
  - Deficient mice
  - Growth failure
  - Hypoglycemia
  - Increased insulin sensitivity
  - One de novo heterozygote reported
  - Severe ID, macrocephaly, short stature, obesity, dysmorphic features
  - Variant not published
  - Variant in a well conserved region
  - Sift: pathogenic
  - Polyphen: benign
  - Mutation taster: disease causing
  - Not in control databases like Exac or 100G

**So what do we do?**
- Go by the laboratory classification officially
- Make a decision as to whether we believe it’s pathogenic or not
- PHENOTYPE INFORMATION IS KEY
- However, if it is a variant make sure the patient knows it is a variant

**Gene known?**
- Gene associated with
  - One de novo heterozygote reported
  - Mutations in a well-conserved region
Functional information

- Strong candidate—we believe likely pathogenic based on evidence, but still a VUS
- A year later
  - Contacted by GeneDx, other cases with similar clinical phenotype
  - Want to publish case series
  - Believe pathogenic

Questions??
Principles of epigenetics

Hans Tómas Björnsson MD PhD
McKusick-Nathans Institute of Genetic Medicine
Johns Hopkins University School of Medicine

Disclosure
• I have no relevant financial relationships to disclose. Today I will not reference unlabeled or unapproved uses of drugs or products in my presentation.

Epigenetic machinery: the genome’s “highlighter”
• Epigenetic marks are modifications of DNA or associated proteins, other than the DNA sequence itself, that are heritable through cell division (mitosis)
• Reversible and affected by the environment
• Add to information content of DNA
  ♦ DNA methylation
  ♦ Histone tail modifications

Methylated cytosine is a potent endogenous mutagen:

DNA methylation: 5-methylcytosine: the fifth base

CpG dinucleotides are overrepresented in CpG islands:

DNA methylation: 5-methylcytosine: the fifth base

DNA hydroxymethylation: the sixth base?

Wu et al. Nature Review Genetics, 2017

Discriminating fact:
Prior methods for DNA methylation don’t differentiate cytosine methylation and hydroxymethylation
Summary (1):

- DNA methylation is the "best" known epigenetic modification, yet we continue to learn new things about this modification;
- DNA methylation is an endogenous mutagen and as a consequence the CpG dinucleotide is underrepresented in the human genome (exception CpG islands) but overrepresented in human mutational databases;

Epigenetics and Chromatin Clinic

- Classical epigenetic disorders
  - Beckwith Wiedemann syndrome
- Disorders of the DNA methylation machinery
  - Rett syndrome
  - Disorders of the histone machinery
  - Kabuki syndrome

The McKusick-Nathans Epigenetics and Chromatin Clinic

Mostly CIS
TRANS

Genetic disorders with epigenetic consequences

The Mendelian disorders of the epigenetic machinery:

Common themes:
1) Intellectual disability (also growth, limbs);
2) Dosage sensitivity: Uniformly caused by the loss of a single allele;

Summary (2):

- The Mendelian disorders of the epigenetic machinery are genetic disorders with epigenetic consequences;
- Common phenotypic features include intellectual disability, and abnormalities of growth;
- Despite known redundancy of the epigenetic machinery, other components with overlapping function are not able to compensate for the loss of a single allele, indicating tight regulation of the levels of these factors and the marks they affect;

A<sup>V</sup> (Agouti<sup>ViableYellow</sup>) mouse model:

Another layer of interindividual variation:

Waterland R et al. MCB 2003

With a certain diet one can affect the number of pseudoagouti mice:

Additional methyl donors

P = 0.008 (t test)

Epigenetics marks can be inherited transgenerationally:

Summary (3):

- Epigenetic marks form an additional layer of variation in addition to genetic variation, can be affected by the environment and in some cases are incompletely erased;
Genomic Imprinting:

Mat. Pat.

Role in placental mammals; Hage hypothesis

Known imprinting disorders:

- Beckwith-Wiedemann Syndrome
- Prader-Willi Syndrome
- Angelman Syndrome
- Pseudohypoparathyroidism 1A
- Pseudohypoparathyroidism 1B
- Transient neonatal diabetes

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Beckwith-Wiedemann Syndrome

- Prenatal overgrowth, macrosomia, organomegaly, macroglossia
- Pancreatic islet cell hyperplasia, Neonatal hypoglycemia
- Linear ear lobe creases
- Midline abdominal wall defects
- Dysmorphic features
- Embryonal tumors (Wilms)
- Hemihypertrophy (or plasia)

Silver Russell Syndrome (SRS):

- Intra-uterine growth retardation
- Small triangular faces, down turned angles of mouth, prominent forehead
- Blue sclera
- Fasting hypoglycemia
- Hypotrophy of limb or a side
- Developmental delay

The molecular mechanisms of BWS/SRS:

Normal

DeBaun et al. AJHG 2002 (BWS);

Causes of BWS:

- Not a single gene but rather a responsible gene domain.
Beckwith-Wiedemann syndrome and phenotype genotype correlations:

- LOI of IGF2/H19 defect
  - Cancer
- LOI of LIT1
  - Lower cancer risk
  - Midline defects
  - Macrosomia
  - Discordant MZ twins

- Uniparental disomy
  - Hemihypertrophy
  - Cancer
  - Hypoglycemia

Uniparental disomy
- Beckwith-Wiedemann Syndrome
- Russell-Silver Syndrome
- Prader Willi Syndrome
- Angelman Syndrome
- Pseudohypoparathyroidism 1A
- Pseudohypoparathyroidism 1B
- Transient neonatal diabetes

Prader Willi Syndrome:
- Neonatal muscular hypotonia/Failure to thrive
- Hyperphagia/Obesity
- Hypogonadism, short stature, small feet/hands
- Behavioural problems
- Mental retardation

Prader Willi Causes:
- Paternal deletion (70%)
- Maternal uniparental disomy (29%)
- Paternal chromosome carries maternal imprint (1%)

Angelman Syndrome:
- Microcephalus, ataxia, absent speech
- Abnormal EEG pattern
- Severe mental retardation
- Frequent laughing
- “Happy puppet sx”

Angelman syndrome causes:
- Maternal deletion (70%)
- UBE3A variants (11%)
- Imprinting defects (4%)
- Paternal uniparental disomy (1%)

Treatment strategies for Angelman syndrome:

Known imprinting disorders:
- Beckwith-Wiedemann Syndrome
- Russell-Silver Syndrome
- Prader Willi Syndrome
- Angelman Syndrome
- Pseudohypoparathyroidism 1A
- Pseudohypoparathyroidism 1B
- Transient neonatal diabetes

Don’t have time.
Transient Neonatal diabetes:


Multi-locus methylation defects

- Frequently seen in association with transient neonatal diabetes;
- Also seen with BWS and RSS but seem rare for PWS and AS;
- Likely a “trans” acting factor that helps maintain imprinting;
- Bottom line: If non-specific feature consider sending multiple imprinting tests.

Does this occur in humans?

Genetically identical mice! Waterland et al. MCB 2003

Discordant MZ twins:

Mz twins discordant for BWS
Haskins Olny et al. AJMG 1988

Mz twins discordant for SRS
Samn et al. AJMG 1990

What about this?

Additional methyl donors
Waterland R et al. MCB 2003

P = 0.008 (f-test)

Environment and imprinting defects:

- Multiple studies suggest over-representation of ART (both IVF and ICSI) in cohorts of patients with some imprinting disorders (Beckwith-Wiedemann Syndrome and Angelman Syndrome)
- Thought to be caused by in vivo cell culture of early embryos or alternatively unmasking of an infertility phenotype;

But surely not this, right?

Incomplete erasure of DNA methylation in humans:

- Epimutations in Prader Willi syndrome (double dose of maternal 15q imprint) have been demonstrated to come exclusively from grandmaternal allele
- This suggests incomplete epigenetic resetting in humans: i.e. a form of transgenerational inheritance in humans.

Summary (4):

- Beckwith-Wiedemann and Russell-Silver Syndromes are clinical and molecular opposites
- Imprinting disorders demonstrate discordant MZ twins, apparent sensitivity to ART and incomplete erasure of epigenetic marks between generations.
**Suggested reading materials:**

- **Textbook**
  - Epigenetics (textbook) by Allis, Jenuwein, Reinberg and Caparos (Cold Spring Harbor Press).

- **Articles**
  - Berdasco M et al. Human Genetics 2013
  - Weissman et al. Seminars in Neurology, 2014
  - Bjornsson HT. Genome Research. 2015

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**https://www.genome.gov/glossary/**

- **Genomic Imprinting:** In genomic imprinting the ability of a gene to be expressed depends upon the sex of the parent who passed on the gene. In some cases imprinted genes are expressed when the are inherited from the mother, in other cases they are expressed when inherited from the father. Unlike genomic mutations that can affect the ability of inherited genes to be expressed, genomic imprinting does not affect the DNA sequence itself. Genomic imprinting affects gene expression by chemically modifying DNA and/or altering the chromatin structure. Often, genomic imprinting results in a gene being expressed only in the chromosome inherited from one or the other parent. When combined with genomic mutations, disease can result. For example, Prader-Willi syndrome and Angelman syndrome are two distinct diseases caused by a deletion in the same part of chromosome 15. When the deletion occurs on the chromosome 15 that came from the father, the child will develop Prader-Willi syndrome. However, when the deletion occurs on the chromosome 15 that came from the mother, the child will develop Angelman syndrome. This occurs because genes located in this region undergo genomic imprinting.

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**https://www.genome.gov/glossary/**

- **Epigenetics:** Epigenetics is an emerging field of science that studies heritable changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism. The word epigenetics is of Greek origin and literally means over and above (epi) the genome.
Definition of CP: Key Points

- Due to lesions, anomalies or non-progressive disturbances of immature brain
- Non-progressive ("static"), but manifestations can change.
  - Dystonia which appears years after acute HIE
  - Hypotonia may evolve into spasticity
- Disorder of motor control
- The definition does not imply cause of lesion, brain malformation or injury
- Should genetic disorders be considered causes of CP?

Causes of Cerebral Palsy

- Multiple etiologies/risk factors →
  - Brain Dysgenesis
  - Brain Injury
- CP is often a multifactorial disorder for which a definitive “cause” is not identifiable
- Various factors environmental & genetic → final common pathways of brain injury

Mechanisms of Brain Insult

**Environmental**
- Teratogenic/toxic (alcohol, mercury)
- Hormonal (hypothyroidism)
- Metabolic
- Infectious (TORCHES)
- Hypoxic-ischemic (fetoplacental insufficiency)
- Traumatic

**Genetic**
- Chromosomal (rearrangement, deletion)
- Triplicates
- Genomic imprinting
- Single gene mutations
- Polygenic interactions
- Mitochondrial DNA abnormalities

Selective Vulnerability

**Regional or cell-specific susceptibility to injury:**
- Occurs during infectious, hypoxic-ischemic or metabolic stress
- Associated with specific imaging patterns
- Recognition refines diagnosis and treatment

Definitions of Cerebral Palsy (CP)

"A persisting but not unchanging disorder of movement and posture, affecting the extremities, the face and head, which is due to a non-progressive disorder of development occurring in early childhood and caused by damage to the developing brain."
-Madsen & Fraser, 1959

"A disorder of movement and posture due to a defect or lesion of the immature brain."
-Bax et al, 1964

"An umbrella term covering a group of non-progressive, but often changing, motor impaired condition secondary to lesions of the brain occurring in the early stages of development."
-Mutch et al, 1992

"Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior by epilepsy, and by secondary musculoskeletal problems."
-Rosenbaum et al, 2005
Importance of Etiologic Diagnosis

- Prognosis
- Recurrence risk
- Treatment of underlying disorder
- Prevention of secondary conditions
- Can stop looking for the “cause”
- Reduction of feelings of guilt, responsibility
- Short and long-term planning
- Legal ramifications

Etiologic Diagnosis: A Challenge

One of the most exacting tests of clinical skill in neuropediatrics is the distinction of the comparatively rare hereditary metabolic diseases from the many non-metabolic diseases and developmental anomalies to which the child’s nervous system is subject.

Consider Further Etiologic Evaluation

- No risk factors for acquired brain injury
- Positive family history
- Normal development followed by regression
- Signs/symptoms of metabolic disorder
- Dysmorphic features
- Dyskinetic CP, Ataxia or Hypotonia
- Unusual MRI findings
- Normal MRI

Family Questions

- Why can’t our child crawl/talk/relate to us?
- Is there a cure?
- What should we do to help?
- Is he going to walk?
- Will she have other problems?
- How will we explain things to him?
- Is this our fault?
- Who will take care of her when we get old?
- How will we pay for all his needs?

History

- Primary concern(s)
- Prenatal/perinatal history
- Medical history
- Behavioral history– phenotypes
- Associated impairments– e.g., vision, hearing
- Symptoms suggestive of progressive disorder
- Family history (draw pedigree)
- Developmental history – trajectory
- Review of Systems

History: Developmental Trajectories

- Normal
- Progressive disorder
- Plateau
- Episodic
- “Non-progressive” disorder

Physical Examination

- Head circumference- velocity of growth
- Skin– skin and brain are both ectodermal
- Dysmorphology- look at family pictures
- Cardiovascular– pulses, rate and rhythm
- Organomegaly– storage diseases
- Sacral anomalies- tethered cord
- Muscle consistency- myopathy
- Head Circumference

Neurocutaneous Examination

Tuberous sclerosis
Neurofibromatosis

Eye Findings

Optic Nerve Atrophy
Optic Nerve Hypoplasia

Etiologic Value of Neuroimaging
1. Establish specific diagnosis
2. Confirm suspected etiology
3. Suggest possible etiologies based on pattern

Genetics 101

Genome:
- 3 billion DNA letters
- >21,000 genes

Karyotype:
46,XX or 46,XY

Mitochondrial Genome
- 16,569 bp
- 37 genes
- High mutation rate
- Multiple copies per cell

Family History

Targeted questions:
- Intellectual disability, autism, LD, DD, CP
- Seizures, migraines, other neurologic problems
- Multiple miscarriages, stillbirth, neonatal death, birth defects
- Early-onset hearing or vision loss
- Psychiatric illness, dementia

Autosomal Dominant
- Multiple generations
- Parent to child transmission
- Males & females affected
- 50% recurrence risk

Ancestry and ethnicity
Consanguinity

FHx – Inheritance Patterns

Bennett et al, 2008; J Genet Couns

Targeted questions:
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Ancestry and ethnicity
Consanguinity
Autosomal Recessive
- Only siblings affected (unless consanguinity)
- Males & females affected
- Both parents carriers
- 25% recurrence risk

X-Linked
- Mostly males affected, females milder
- Only mother’s side
- No transmitting males
- 50% recurrence risk for male offspring

Mitochondrial (mtDNA)
- Maternal inheritance, no transmitting males
- Both genders affected, wide variability
- High recurrence risk

Myths & Confounders
- Myths
  - All genetic disorders are inherited
  - Negative FHx means the condition isn’t genetic
- Confounders
  - Variable expressivity
  - Reduced penetrance
  - De novo mutations
  - Red herrings

Cytogenetics - Chromosomal Microarray
- Molecular (DNA) testing
  - Single gene analysis
  - Multi-gene disease panels
  - Whole exome sequencing
  - Whole genome sequencing

Finding a laboratory: www.genetests.org
- Do your homework – molecular test?
- Shop around – prices vary widely between labs
- Buyer beware – read the fine print
  - Methodology e.g. full sequencing, targeted mutation, deletion
  - Quoted detection rate
- Gene panels – do you really need the whole panel?
- Not sure? Call the laboratory genetic counselor
- Check insurance!!!

Disease categories masquerading CP
- Brain malformations
- Diseases involving basal ganglia
- White matter diseases
- Pseudo-TORCH syndromes
- Spastic Paraplegias
- Genetic Ataxias
- Disorders of CNS neurotransmitters
Brain Malformations

- Isolated brain malformation vs multiple congenital anomaly syndrome
- Environmental and genetic causes
- Some malformations tend to occur together
- Misclassification is common
- Accurate diagnosis helps with prognosis, associated problems, and genetic counseling regarding future pregnancies

Brain Malformation #1

- Complete agenesis, partial agenesis, hypogenesis, dysgenesis
- Isolated ACC or part of other brain malformation syndrome
  - Holoprosencephaly
  - Lissencephaly
  - Septo-Optic Dysplasia
  - Chiari II malformation
  - Dandy-Walker malformation
  - Aicardi Syndrome

Brain Malformation #2

One day-old newborn

Massive hydrocephalus due to Aqueductal Stenosis

Brain Malformation #3

X-linked Hydrocephalus

- X-linked: due to L1CAM mutations
- Associated with cortical malformations, thalamic fusion
- Hydrocephalus due to aqueductal stenosis
- CRASH: callosal hypoplasia, mental retardation (intellectual disability), adducted thumbs, spastic paraplegia and X-linked hydrocephalus

Brain Malformation #4

Joubert Syndrome / Molar Tooth Disorders

Joubert Syndrome

- Small, dysplastic cerebellar vermis
- Abnormal folial pattern
- Narrow isthmus (junction of mesencephalon and pons)
- Midline cleft separating two areas of vermis
- Typical imaging appearance:
  - "molar tooth" appearance of midbrain on axial images
  - 4th ventricle situated high, at midbrain-pons junction
  -Absent septum pellucidum
  - Fused fornices

Joubert Syndrome & Related Disorders (Molar Tooth Disorders)

- Associated with
  - Hydrocephalus
  - Hypotonia / ataxia
  - Abnormal breathing pattern: hyperpnea and central apnea
  - Nephronophthisis
  - Polydactyly
  - Retinopathy

- Genetics
  - Autosomal recessive
  - Ciliopathy
  - Multiple genes

Agenesis of the Corpus Callosum

Dandy-Walker Malformation with Hydrocephalus

X-linked mutations (หาไร)

Associated with many syndromes
Holoprosencephaly (Spectrum)

Holoprosencephaly Disorder of Diverticulation-Cleavage
- Continuum of abnormality
- Recognized forms
  - Alobar
  - Semilobar
  - Lobar
  - Middle Interhemispheric Variant

Semilobar Holoprosencephaly
- Partial but interrupted brain diverticulation
- "H-shaped" monoventricle - Occipital and temporal horns
- Rudimentary falx and interhemispheric fissure
- Partial or complete "fusion" of basal ganglia

Lobar Holoprosencephaly
- Nearly complete brain cleavage
- Absence of normal gyral pattern - Squared-off or box-like frontal horns
- Separation of basal ganglia
- Squared-off or box-like frontal horns
- Separation of basal ganglia
- "Fusion" inferior frontal lobe

Middle Interhemispheric (MIH) Variant of Holoprosencephaly

Clinical Presentation of HPE
- Motor delay
- Mixed movement disorder
  - Dystonia
  - Hypotonia
  - Spasticity
- Range of intellectual function
- Epilepsy
- Hypothalamic-pituitary dysfunction

Genetic Causes of HPE
- Chromosomal abnormalities (40 - 50%)
- Microdeletions (10%)
- Syndromes (5 - 10%)

- HPE Gene Mutations (25%)
  - Familial Holoprosencephaly
  - Polygenic (two hits)

- X-linked
- DICK (Doublecortin)
  - Affected more anteriorly
  - Females have subcortical band heterotopia

- Autosomal
  - ARX: Abnormal genitalia
  - Spectrum lissencephaly to non-syndromic LIS/MR
  - Females have callosal agenesis
- Dominant (DeNovo)
- LIS1 affected more posteriorly
- Recessive
  - CRMP5 with cerebellar hypoplasia
  - ULB2 (alpha-tubulin) mutation

Type 1 Lissencephaly
Classical lissencephaly is a developmental brain malformation characterized by abnormal neuronal migration, 4-layer cortex, and smooth (or relatively smooth) brain surface, i.e. agyria/pachgyria
**Miller Dieker Syndrome**
Deletion 17p13.3 including LIS1

**Heterotopic Gray Matter**
Heterotopias
- Subcortical band heterotopia
  - Can be seen with DCX and LIS1 mutations
- Bilateral, nodular subependymal heterotopias: Filamin 1 gene (FLNA) mutations
- Microcephaly with periventricular nodular heterotopias: ABHD2 mutations

**Brain Malformation #6**
Unilateral, Open-Lip, Schizencephaly

**Schizencephaly**
- Clefts in the brain parenchyma that extend from the cortical surface to the ventricle (pia to ependyma), lined by dysplastic gray matter
- Frontal and parietal clefts near sylvian fissures are most common
- Type 1 closed lip: small with walls apposed to each other
- Type 2 open lip: large, gray matter-lined, fluid-filled cerebrospinal fluid clefts
  - Can mimic hydranencephaly

**Brain Malformation #7**
Lepto-Optic Dysplasia (LOD) / De Morsier Syndrome
- Heterogeneous disorder characterized by hypoplasia of optic nerves/tracts, absent septum pellucidum, typically hypothalamic-pituitary dysfunction.
- Can be associated with schizencephaly, heterotopias, callosal dysgenesis, cortical dysplasia
- Genetics:
  - Most cases sporadic
  - Occasionally autosomal dominant or recessive
  - Rare HESX1 gene mutations

**Brain Malformation #8**
Polymicrogyria (PMG)
- Malformation of cortical development
- Characterized by multiple small gyri with abnormal cortical lamination
- Distribution: e.g. perisylvian, frontal, parietal, etc.
- Non-genetic: congenital infections; cerebral ischemia 2° to placental problems, maternal drug use
- Syndromes (many) – e.g. Aicardi, congenital muscular dystrophies (Merosin deficiency, Fukuyama), Zellweger
- Chromosome abnormalities (many) – e.g. 22q11 deletion
- Single genes: (many)
  - ARX, DCX, WDR62, GPR56, TUBB2B, SRPX2

**Non-syndromic Mendelian PMG**

**Perisylvian Polymicrogyria**

**Brain Malformation (PMG)**
- Worster-Drought Syndrome and Perisylvian Disorders
  - Worster-Drought syndrome (WDS): clinical phenotype of congenital pseudobulbar paresis ± additional features
  - Congenital Bilateral Perisylvian Syndrome (CBPS): bilateral perisylvian polymicrogyria, epilepsy, pseudobulbar paresis ± additional features
  - "mild" sequelae: CP, learning/cognitive disabilities, autism spectrum disorders, hyperactivity/ADHD, contractures

**Familial and Genetic Associations in Worster-Drought Syndrome and Perisylvian Disorders**

- Worster-Drought syndrome (WDS)
- Congenital Bilateral Perisylvian Syndrome (CBPS)
- "mild" sequelae: CP, learning/cognitive disabilities, autism spectrum disorders, hyperactivity/ADHD, contractures
DISEASES WITH ABNORMAL BASAL GANGLIA

Mitochondria

1500 genes regulate mitochondria
37 genes encoded by mtDNA, the remainder by nuclear DNA

Mitochondria

Mitochondrial Genome

- Total size = 16,569 bp
- 37 genes encode:
  - 2 ribosomal RNAs
  - 22 transfer RNAs
  - 13 OXPHOS proteins

Manifestations of Mito Dz

- CP-like presentations:
  - Perinatal depression
  - Neonatal seizures
  - Intrapartum
  - Developmental delay
  - Hypomyelination
  - Episodic/progressive dystonia
  - Slowly progressive spastic paraplegia
  - Microcephaly
  - Vermian hypoplasia
  - Seizures
  - Myopathy

Some forms improve over time

Selective vulnerability in Mitochondrial Diseases

- Basal Ganglia
  - (often the globus pallidus)
- Thalamus
- Cerebellum
- Optic nerves
- Inner ear hair cells

Glutaric Aciduria, Type 1

- Glutaric Aciduria type I and II now tested in newborn screening in many states
- Due to mutation in glutaryl-CoA dehydrogenase GCDH
- GA1 is usually acute but can be subtle in onset
- Macrocephaly @birth, Opisohphalous, dystonia and striatal necrosis
- Notably normal IQ
- Usually not progressive after initial episode

Glutaric Aciduria 1

Neurodegeneration with Brain Iron Accumulation (NBIA)

- Pantothenate-Kinase associated neurodegeneration (PKAN)
- Neuroferritinopathy (NFT)
- Aceruloplasminemia (ACP)
- Fatty acid hydroxylase (FA2H)
- Infantile Neuroaxonal Dystrophy (iNAD)
- Others...
**PKAN**
- Autosomal recessive, PANK2 gene, most common NBIA
- Severe dystonia involving orobuccal muscles
- Developmental delay
- Retinitis pigmentosa
- Intellectual disability
- Seizures

Atypical form – slower progressive over the first 2 decades.

**Infantile neuroaxonal dystrophy**
- Autosomal recessive, PANK2 gene
- Developmental delay
- Initially profoundly hypotonic later very spastic
- Loss of vision
- Peripheral neuropathy
- Cerebellar atrophy

**Infantile neuroaxonal dystrophy**
- Autosomal recessive, PLA2G6 gene
- Developmental delay
- Initially profoundly hypotonic later very spastic
- Loss of vision
- Peripheral neuropathy
- Cerebellar atrophy

**Succinic Semialdehyde Dehydrogenase (SSADH) deficiency**
- Also known as 4-hydroxybutyric aciduria
- Relatively nonprogressive encephalopathy
- Hypotonia
- Developmental delay
- Ataxia
- Epilepsy
- Hyperactivity
- OCD
- Infrequently chorea, dystonia

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**Lesch-Nyhan Disease**
- HPRT1 gene (hypoxanthine phosphoribosyltransferase 1)
- X-linked inheritance
- Characterized by overproduction and accumulation of uric acid causing gouty arthritis and kidney stones in addition to neurologic sequelae
- Onset in infancy or early childhood
- Often diagnosed as CP
- Choreoathetosis
- Self-mutilation including self-biting and head-banging

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**Thiamine Transporter Deficiency (SCL19A3)**
- = Biotin-responsive basal ganglia disease but mechanism of Biotin action unclear
- Severe developmental delay
- Infantile spasm
- Hypotonia
- Spastic quadriplegia
- Dystonia

**Biotinidase Deficiency**
- Included in newborn screening
- Treatable with Biotin
- Biotin important cofactor for many enzymes
- Seizures, hypotonia, dev delay
- Organic aciduria
- Hearing and vision loss
- Skin findings – alopecia, eczema

**Miscellaneous Basal Ganglia Diseases**
- Wilson Disease
- Huntington Disease
- Leukodystrophies
- Pseudo-TORCH syndrome
WHITE MATTER DISEASES

Disorders of Myelination

- **Hypomyelination**: Reduced quantity of myelin for age.
- **Delayed myelination**: Myelination is progressing but delayed for chronological age. A follow-up MRI study would show increase in myelin deposition both in amount and distribution that would be appropriate for a lower age group.
- **Demyelination**: Loss of prior acquired myelination.

**Pelizaeus Merzbacher Disease (PMD)**

- X-linked disorder affecting boys, spasticity, with seizures or peripheral Neuropathy due to duplications or other mutations in PLP1 gene.
- Can present at birth with severe hypotonia
- Striking nystagmus
- Wide phenotypic range, some individuals are able to walk.

**PMD-like disease**

- Autosomal recessive (also affecting girls)
- Due to mutations in gap junction protein alpha 12 (GJA12)
- Usually severe seizures, but milder clinical course than classic PMD.

**Monocarboxylate Transporter 8 Deficiency**

- MCT8-specific thyroid hormone cell transporter deficiency
- a.k.a Allan-Herndon-Dudley syndrome, X-linked
- Congenital hypotonia
- Intellectual disability
- Severe dysarthria or no speech
- Progressive spastic quadriplegia
- Dystonic/thetoid movements
- Paroxysms/Dyskinesias
- Seizures (25%)
- Craniofacial appearance (myopic face, large ears, etc)

**Pathway & Mechanism**

Thyroid hormone transport & deiodination in a target cell

Source & transport of T3 in the brain

ALWAYS CHECK T3 in addition to TSH/T4

Hypothyroidism

**Deficiency of Hypoxin (a newly identified membrane protein)**

Atrophy of basal ganglia

**Hypomyelination with congenital cataracts**

**Hypothyroidism , hypodontia & hypogonadotropic hypogonadism (4H syndrome)**

- Hypotonia
- Progressive ataxia
- Initially normal cognitive development
- POLR3A mutation - codes for the largest subunit of RNA polymerase III
Sialic Acid Storage Disease
- Due to mutations in Sialin = transporter of sialic acid in lysosomes (Autosomal Recessive)
- Hypomyelination
- Neonatal hypotonia
- Ataxia
- Nystagmus
- Seizures
- Spastic quadriplegia
- Have either Sialic Aciduria or elevation in CSF only

EIF2B associated vanishing white matter / Cree Leukoencephalopathy
- Gene involved in translation of proteins
- Usually presents during childhood but also infantile form in Cree Native Americans
- Can present at birth with HIE, microcephaly, seizures
- MRI shows lack of myelin in entire forebrain

Krabbe Disease = Globoid Cell Leukodystrophy
- Due to GALC mutations (lysosomal enzyme, autosomal recessive)
- Early infantile form can present within the first few weeks
  - Opisthotonus
  - Severe sussiness
  - Peripheral neuropathy
  - Optic nerve hypertrophy
- Calcifications may develop in cerebellar nuclei and thalams

Metachromatic Leukodystrophy
- Due to mutations in Arylsulfatase (lysosomal enzyme, autosomal recessive)
- Infantile form can present within the first few months with hypotonia, global delay, spasticity later on may be slowly progressive

Peroxisomal Biogenesis Disorder/Zellweger Spectrum
- Autosomal recessive genes of peroxisomal assembly (PEX family)
- Wide clinical phenotype
- Severe spectrum is Zellweger with neonatal hypotonia, dysmorphic features, large fontanel, liver-kidney failure
- Milder variants
  - Neonatal adrenoleukodystrophy
  - Infantile Refsum’s disease
  - Non-syndromic developmental delay
- Ruled out by plasma very long chain fatty acid testing

Destructive white matter diseases mimicking cystic PVL

Sulfite Oxidase Deficiency
- Autosomal Recessive
- Neonatal Seizures
- Severe hypotonia
- Can look like “HIE” in clinical course
Mitochondria

Pyruvate Dehydrogenase Deficiency
- Small for gestational age
- Low Apgars
- Lethargy, poor feeding
- Hypotonia
- Abnormal eye movements
- Episodic dystonia
- Some are dysmorphic
- 90% X-linked

Fumarase deficiency
- Can present with prenatal cysts
- Opisthotonic newborn
- Often born mildly premature
- Fumaric aciduria
- Later on degenerative course

PSEUDO-TORCH DISEASES

Aicardi-Goutieres Syndrome
- Autosomal recessive inheritance
- Early onset encephalopathy, seizures, thrombocytopenia, organomegaly, fever
- CSF: ↑WBC (<4), ↑interferon-alpha (>10pg/mL), ↑pterins (neopterin).
- Gene defects: 5 genes identified
- Calcifications

Cerebroretinal microangiopathy with calcifications and cysts (CRMCC).

Band-like calcifications and polymicrogyria
- OCLN gene, autosomal recessive
- Early-onset seizures
- Severe microcephaly
- Profound delay
- Calcifications
- Polymicrogyria

Diseases with delayed myelination
- Usually primarily neuroaxonal disorders
  - Neuronal ceroid lipofuscinosis (Batten Disease)
  - Sanfilippo syndrome (Mucopolysaccharidosis 3)
  - Mucosidosis
  - Fucosidosis
  - Tay-Sachs Disease
  - Mitochondrial disorders
  - Biotinidase Deficiency
SPASTIC PARAPLEGIAS

Hereditary Spastic Paraplegias
- >30 types
- Progressive spasticity and weakness
- SPG4, SPG13A, SPG7, SPG31 start early in life
- SPG2 = variant of PMD
- SPG35 = FA2H
- SPG1 = L1CAM

Arginase Deficiency
- Auto recessive disorder of urea cycle, ARG1 gene
- Episodes of hyperammonemia are subtle
- Part of newborn screening in many states
- Slowly progressive spastic diplegia
- Intellectual disability

GENETIC ATAXIAS

Spinocerebellar Ataxia
- Autosomal Dominant
- Triple repeat with anticipation
- SCA 2 & 7 can start in early infancy
- Early presentation of other SCAs also reported

Clinical classification of SCAs

Ataxia Telangiectasia
- Recessive, ATM gene
- Developmental delay
- Ataxia
- Choreaathetosis
- Abnormal eye movements
- Immunodeficiency with recurrent infections, risk for cancer
- Telangiectasias may not be present in infancy
- Short stature
- Elevated alpha-fetoprotein

Angelman Syndrome
- Normal as newborn
- Severe cognitive/motor delay
- Epilepsy
- Postnatal microcephaly
- Fair complexion, hypopigmentation
- Large mouth, widely spaced teeth
- Severe speech impairment
- Ataxic gait and/or tremulousness
- Fascination with water
- Methylation analysis (>70% detection rate), followed by UBE3A sequencing. > FISH analysis outdated.

Miscellaneous Ataxias
- Joubert syndrome
- Congenital Disorders of glycosylation
- Mitochondrial diseases
- Episodic Ataxias
**Disorders of CNS Neurotransmitters**

- **Monoamine Metabolic Pathways**
  - Tyrosine hydroxylase (TH)
  - Tryptophan hydroxylase (TPH)
  - Tetrahydrobiopterin (BH4)
  - Aromatic L-amino acid decarboxylase (AADC)
  - Pyridoxal 5-phosphate (PLP)
  - Catechol-O-methyltransferase (COMT)
  - Monoamine oxidase (MAO)
  - Homovanillic acid (HVA)
  - 5-Hydroxyindoleacetic acid (5-HIAA)
  - Dopamine β-hydroxylase (DBH)
  - Arylamine N-acetyltransferase (NAT)
  - Phenylethanolamine N-methyltransferase (PNMT)
  - Acetylserotonin O-methyltransferase (HIOMT)

**Cerebral Folate Deficiency**
- Multiple etiologies
  - Folate Transporter Gene mutation
  - Antibodies against Folate Transporter
  - Mitochondrial diseases involving complex I function
- Reduced 5-Methyltetrahydrofolate in CSF
- Not related to MTHFR gene mutation
- Variable phenotype including
  - Spastic diplegia
  - Dystonia
  - Intellectual disability
  - Myopathy
  - Sleep
  - Seizure
- Patients may respond to Folinic Acid (Leucovorin)

**Case Reviews**

2 year-old boy with...
- Profound hypotonia
- Global developmental delay
- Mild dysmorphic features
- Uncomplicated pregnancy & birth (full-term)
- Hypotonia & feeding difficulties at birth, failure to thrive
- Prior work-up (all normal):
  - Fetal newborn screening
  - Karyotype, Angelman methylation, MECP2 deletion
  - CMP, CK, TSH, T4

MRI at 1.5 years

8/21/2017
KXI Evaluation @ 2years
- Plasma amino acids, urine organic acids, VLCFA, lactate, pyruvate, ammonia, CK, CDG → all normal
- Thyroid studies:
  - High T3 = 3.66 ng/ml (0.80 – 2.00)
  - Low T4 = 0.5 mg/dl (0.7 – 1.8)
  - TSH = 4.47 uIU/ml (0.50 - 4.50)
- MCT8 gene sequencing:
  - Hemizygous frameshift mutation (c.1696_1703del8)

8y boy with dystonic CP + ptosis
- Normal birth history
- Developmental delay
- Truncal hypotonia
- Felt to be cognitively normal
- MRI of the brain x2 normal
- EMG NI
- Vibein normal but ptosis
- No history of regression
- Mild response to L-Dopa but became more dystonic as dose was increased

CASE: 10 year-old girl with...
- Limited info about medical history
  - Lives in nursing home, in State custody
  - Records: “Job syndrome” (hyper Ig syndrome)
  - MD report states: “CT consistent with sequelae of HIE”
  - Features: L. osteopetrosis, right hip/valgus & hip dislocations, scoliosis;
  - Died after a severe ITU, now G-tube feeding
- Examination:
  - HT: 142.6 kg (8%), HT=54.7cm (44%), HC=49.5cm (<2%
- Decreased levels of HVA, 5HIAA, HIAA
- karyotype:
  - FXY+ del/dup
- Dopa but became more dystonic
- Complex medical history
- **Presented to KKI @ 6.5 years**
- **Birth:**
  - 36 weeks ago, birth weight: 6lb 11oz, HC = 33 cm
- **Hx:**
  - Seizures, Drooling
  - Mild hypothyroidism
  - Microcephaly
  - **Examination:**
    - **Hx:**
      - 0-10 years old for evaluation of cerebral palsy
      - 6-10 year old sister, 2-3 year old half sister, 6-8 year old pat half brother
- **Development:**
  - Mom says normal until 8-9 months, then regression and lost all skills
- **Family History:**
  - Non-contributory; siblings and parents healthy

Monoamine Metabolic Pathways

1. CSF results...
2. Enzyme results...
3. Genetic results...

Homozygous DDC mutation c.665T>C (p.L222P)

CSF Neurotransmitters

<table>
<thead>
<tr>
<th>CSF Neurotransmitters</th>
<th>Normal</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-methyltetrahydrofolate</td>
<td>105</td>
<td>40 – 28</td>
<td>ng/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.2</td>
<td>0.5 – 2.7</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Homovanillic acid</td>
<td>6</td>
<td>16 – 318</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Homovanillinic acid</td>
<td>53</td>
<td>218 – 452</td>
<td>mmol/L</td>
</tr>
<tr>
<td>3-O-methyldopa</td>
<td>661</td>
<td>&lt;100</td>
<td>ng/L</td>
</tr>
<tr>
<td>Neopterin</td>
<td>10</td>
<td>7 – 40</td>
<td>ng/L</td>
</tr>
<tr>
<td>Tetrahydrobiopterin</td>
<td>22</td>
<td>9 – 40</td>
<td>ng/L</td>
</tr>
</tbody>
</table>

Early History
- **Present:**
  - Mother: healthy 20 year old G2 P1011; no complications, infection, exposure; normal ultrasounds
  - Birth: PTD, no complications, Agaps = 9 + 9
    - Congenital valgus deformity
- Development: Mom says normal until she had her first seizure @ 8-9 months, then regression and lost all skills
- Family History: non-contributory; siblings and parents healthy
  - 12 yr-old sister, 5 yr-old mat½ sister, 6 yr-old pat½ brother
- Metabolic study: Homozygous DDC mutation c.665T>C (p.L222P)
- Initial presentation: Aged 2 yrs for evaluation of cerebral palsy
- History of motor delays, diagnosed with CP
- Symptoms (dysphagia, increased tone) have worsened recently
- Extensive prior evaluations have been unrevealing, except for unusual lesions on brain MRI of unknown significance
- Parents want to know:
  - 8y boy with dystonic CP + ptosis

Work-Up
- MECP2 sequencing + del/dup
- CHENG sequencing + del/dup
- FGND2 sequencing
- Carbohydrate deficient transferrin
- MNS TEC
- Argelman methylation testing
- SNP chromosome microarray
- Brain MRI + MRS....
History
- Born full-term, no pregnancy/neonatal complications
- Always healthy, no major medical problems
- Normal early developmental milestones, walked at 22 months
- First concerns with fine and gross motor – “uncoordinated”
- Poor fine motor skills, difficulty climbing stairs, frequent tripping/falling
- Speech difficult to understand, but very good receptive language
- Very bright – no cognitive issues/ID
- No developmental regression

Genetic test results
- Suspected pantothenate kinase-associated neurodegeneration (PKAN) based on clinical hx and MRI findings
- PANK2 gene sequencing:
  - homozygous for known pathogenic mutation in exon 1 (c.215_216insA)
  - Frameshift creates premature stop codon 47 amino acids downstream

Conclusion
- Genetic Disease can mimic cerebral palsy.
- Careful history and examination provide important clues towards the etiology.
- Neuroimaging is a pertinent diagnostic test for categorizing the neural systems/networks involved.
- Advances in genetic testing modalities provides an opportunity to identify etiologies in CP.

Abnormal Basal Ganglia MRI mimicking CP
- Mitochondrial disorders including glutaric aciduria
- Neurodegeneration with brain iron accumulation
- Succinyl-Semialdehyde dehydrogenase
- Thiamine Transporter Deficiency (SLC19A3)
- Dihydropyrimidinase Reductase deficiency (variant of atypical PKU)
- Pseudo-Torch
- Leukodystrophies
- Wilson and Huntington Disease can very rarely present in early childhood.

Hypomyelination mimicking CP
- Pelizaeus Merzbacher Disease (PMD)
- PMD-like Disease
- Monocarboxylate Transporter 8 deficiency
- Cree Leukoencephalopathy
- Hypomyelination and Congenital Cataract
- Hypomyelination with hypodontia
- Sialic Acid Storage Disease

Leukoencephalopathy with brainstem and spinal cord involvement, and lactate
MRS in leukoencephalopathy with brainstem and spinal cord involvement and lactacidosis
Causally
Mitochondrial aspartyl-tRNA synthetase deficiency

Genetic Disease mimicking cystic PVL
• Sulfite Oxidase Deficiency/Molybdenum Cofactor Deficiency
• Mitochondrial Disorders
  – Fumarase deficiency
  – Pyruvate dehydrogenase Deficiency
  – Mitochondrial Depletion syndrome
• RNASET2-Deficient CMV like Leukoencephalopathy

RNASET2-deficient cystic leukoencephalopathy resembles congenital cytomegalovirus brain infection.
• Autosomal recessive disorder
• Loss-of-function mutations in the gene encoding the RNASET2 glycoprotein lead to cystic leukoencephalopathy.
• Indistinguishable clinical and neuroradiological phenotype from congenital cytomegalovirus infection
• Both an inborn failure of RNASET2 activity or the prevention of RNase L activation by CMV would result in raised levels of ssRNA, stimulating a comparable immune response

Spastic Paraplegias mimicking CP
• Hereditary Spastic Paraplegias
• Arginase deficiency
• Congenital isolated Vitamin E deficiency (very rarely in infancy)

Genetic Testing
• Cytogenetic testing
  – Karyotype
  – Fluorescent in situ hybridization (FISH)
  – Chromosomal microarray

Chromosomal Microarray
• Method for detection of Copy Number Variants (CNV)
  – CNV = gains or loss of genetic material
  – Resolution = 20,000 bp
  – Diagnostic yield = 15-20%
• Now recommended as first-tier test for patients with:
  – Global developmental delay
  – Intellectual disability
  – Autism spectrum disorders
  – +/- congenital anomalies or dysmorphic features

Chromosomal Microarray
• Older microarray platforms = BAC and Oligo (“CGH”)
• Newer technology is SNP-based
  – SNP = single nucleotide polymorphism
  – Determines copy number and genotype
  – SNP array will detect copy-neutral loss of heterozygosity due to uniparental disomy or parental consanguinity
Developmental Origins of Health and Disease
Mary L. Leppert MB BCH

DEATH RATES IN GREAT BRITAIN AND SWEDEN
SOME GENERAL REGULARITIES AND THEIR INTERPRETATION

• "Each generation after the age of 4 years seems to carry along with it the same relative mortality throughout adult life and even into the extremes of old age"

• "We may postulate that, constant hereditary endowment being assumed, the health of the child is determined by the environmental conditions existing during the years 0-15, and that the health of man is determined preponderantly by the physical constitution which the child has built"

Associations: Prevention, Mitigation, and Cure – Contributions of a Century

“Millennial Morbidities”

• Lyndon B. Johnston - 1964 War on Poverty
• 2011 AAP Committees identified the “Millennial Morbidities”
  – Mental Health issues
  – Adverse effects of technology
  – Obesity
  – Economic Disparity
  – Racial/Ethnic Disparity

Poverty
• The Abecedarian Program and the Perry Preschool Program- Early Intervention programs of children of severe disadvantage
• Adult Outcomes:
  – Scored higher on academic measures
  – Reached higher educational levels
  – Earned higher wages
  – Were less likely to require special education services
  – Were less likely to have trouble with the law.

Toxic Stress
• An exaggerated or prolonged tension that leads to a prolonged physiological response that is unabated because of a compromised or absent adult reassurance or support
• Ecdobiodevelopment: the concept that brain development is in part driven by interactions between the biology (genetic predisposition) and the ecology (social and physical environment).
• Recent studies suggest that we must look beyond genotype and environment and appreciate the influence that environment has on gene expression; brain development may be a determinant of learning, social, and physical wellbeing

Poverty/stress
• 10 year longitudinal Preschool Depression study of 145 children
• 3-6 evaluations over 10 years
  – Child and adolescent psychiatric assessments which capture stressful/traumatic experiences
  – Blinded observations of peer-child interactions
• Poverty and stress in early childhood were associated with smaller volumes of amygdala and hippocampus in early adolescence, both areas of stress regulation and emotional processing, are sensitive to early adversity.
• But: positive adult relationships have a protective effect on hippocampal volume, suggesting that the effects of poverty can be mediated by caregiver behavior or support.
Environment of Early Childhood: Influence on Language Development

- The idea that language development is dependent solely on either a predetermined genetic potential for language ability, or on environmental exposure is naïve.
  - Predetermined Genetic Potential
  - Environment (largely due parent or caregiver traits) can shape, remediate, or prevent language ability

Language Environment

- Family Structure
  - Single caregiver homes
  - Birth order
  - Adoption
- Caregiver Characteristics
  - Education/Profession
  - Mental Health
  - Parent Child Interactions
  - Stress
- Childcare setting
  - Adult/child ratio
  - Childcare provider training
  - Bilingual settings
- Socioeconomic Status
- Adverse Childhood Experiences
  - Abuse/Neglect
  - Substance use
  - Un or under-employment
  - Family stress
  - Parental depression
- Physical exposures
  - Tobacco
  - Lead

Language Mitigators

- Language Exposure
  - Number of words
    - Higher SES/Professional - 215,000 words/100 hrs
    - Lower SES - 62,000/100
    - 32 million words/4 years
  - Sophistication of words
  - Decontextualized
  - Conversational turns
  - Simultaneous bilingualism

Influences on Language Development

There appears to be an impact of environmental influences on genetic expression, as there is growing evidence of neurobiological consequences of environmental exposures that may further change the way we approach language development.

Influences on Health and Disease: Fetal Environment

- Mitigators
  - Intended and unintended

The Barker Hypothesis

- The Barker hypothesis holds that the pre-conceptual and intrapartum health of pregnant women determines the health of not only just the fetus and infant, but also for that offspring in adulthood.

Hertfordshire Study

- 5654 men born 1911-1930
  - 1186 of whom had died by 1987
  - There were no differences in birth weight means by social class.
  - Birth weight, weight at 1 year, death by disease type, and standard mortality ratios were evaluated.
  - Birth weight < 5.5 lbs at birth had the highest SMR for Ischaemic heart disease and obstructive lung disease.
  - The highest SMR was for men with birth weight < 5.5 lbs and 1 year weight < 18 lbs.

  "The combination of poor prenatal and postnatal growth led to the highest death rates from ischaemic heart disease. We conclude that poor growth in prenatal or early postnatal life strongly influence risk of ischaemic heart disease.”

Barker 1989
Helsinki Birth Cohort Study HBCS

- HBCS II: 1934-1944, >13,000 subjects
- Using a Ponderal Index (kg/m^3) as a measure of thinness at birth:
  - Low PI and low SES influence the risk for CHD, but the low PI is independent of and magnifies the risk of CHD.
- One aim of HBCS II was to see if childhood growth mitigates the effect of low growth in utero.
- Low birth weight increases risk of CHD
- Low weight, height and BMI at 1-2 years further increases risk CHD
- Low SES in childhood compounds risk of CHD.
- Late “catch up” growth for children with low birth weight increases the risk of CHD.

Eriksson, 2016

Fetal Programming

- "A process whereby a disturbance of the environment at critical stages of development of regulatory systems and their target tissues, alters development in such a way as to permanently change functional capacity and predispose the individual to disease later in life.”

> Pitcher et al. 2006

Malnutrition

- Poor nutrition, either because of the absence of essential nutrients or because of the excess of inappropriate nutrition, has a clear long term effect on the developing fetus.
  - Folate and choline influence neural tube formation
  - 812 impacts DNA methylation
  - Tryptophan is an essential for neurotransmitters
  - Zinc for neural migration
  - Iron is essential for appropriate cognitive, motor and behavioral development.

Mechanisms of Malnutrition? Fetal Programming

- Slow fetal growth may alter liver growth and metabolism, resulting in smaller livers and less efficient lipid metabolism. HBCS study: 20% of 62 year olds on lipid lowering meds, with low birth weight over represented in this group.
- Low birth weight also causes smaller pancreas and fewer beta cells, poor vascularization of beta cells.
- Type 2 Diabetes: PPARγ2 high risk allele associated with autism
- Maternal Body Composition and Fetal Programming

Maternal obesity during pregnancy is associated with higher rates of congenital defects and miscarriage.
- HBCS II: High maternal BMI is associated with higher rates of CHD, T2D, and cancers in offspring independent of SES.
- Low maternal BMI associated with low % fat in adult offspring.
- High maternal BMI associated with higher BMI infants and in adult offspring.
- High BMI associated with higher rates of congenital defects and miscarriage.
- Maternal obesity: associated with higher rates of preterm birth, SGA infants, and altered fatty acid and congenital malformations.
- Maternal Body Composition and Fetal Programming

- Increased BMI in pregnancy is associated with higher rates of CHD.
- Mice on high fat diets have higher rates of fatty liver disease and glucose intolerance.
- Metabolism

- Diabetes
  - Hyperglycemia is a teratogen
  - Infants of diabetic mothers have higher rates of Type 2 Diabetes: PPARγ2 high risk allele associated with autism
- Obesity
  - Increased fatty acids and glucose
  - Increased neurohormones and inflammatory markers
  - High BMI associated with decreased DNA methylation
- Infection

- Maternal infection: Pathogen or inflammatory response: higher rates of CNV and Autism
- Nature and timing of infection influence outcomes (periods of vulnerability)
  - CMV
  - Varicella
  - HIV
  - Zika
- Chronic Maternal Conditions

- Seizures
  - Maternal seizure activity: associated with higher rates of preterm birth, SGA infants, and altered fatty acid and congenital malformations.
  - Maternal effects on pregnancy, effect of malignancy on fetus
- Cytotoxic drugs are teratogenic but infants exposed to chemotherapeutic agents who escape embryopathy are often small for gestational age.
Difficult birth and premature birth are not always accidental happenings, but may frequently be results of a deeper cause, or its expressions, without being the actual etiological factor. Thus it may well be possible that the same pathogenic factors that rendered intrauterine environment abnormal also extended their influence to parturition; abnormal birth is then the final result of abnormal pregnancy.

Sigmund Freud, 1897