Genetics Across the Lifespan – Putting It All Together

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Thursday, November 29
12:00 - 12:30pm Central

Time Out for Genetics Webinar Series
Presented by the Genetics in Primary Care Institute
Faculty

• Melissa Parisi, MD, PhD, FAAP, FACMG
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Learning Objectives

1. Understand how genetics, epigenetics, and environment affect human development over the life cycle

2. Appreciate the life stages that may predispose to genetic and epigenetic influences on health and disease

3. Recognize that some specific pediatric disorders and syndromes are due to errors in epigenetic regulation at imprinted genes
From DNA to person

genes

epigenetic changes

environment

random events

http://www.mondolithic.com/?m=200904&paged=2
How important is the DNA sequence?

100% Identical genomes can produce widely divergent phenotypes
Epigenetics

• All heritable (or stable) changes in gene expression that are not coded in the DNA sequence itself:
  – A layer of regulation of gene expression
  – Allows for differentiation and specialization
  – Allows for plasticity and responsiveness on a individual lifetime scale
  – But still allows for heritability and stability of the changes
Two main epigenetic mechanisms

DNA methylation

Histone modification

“Epigenetics – What Your Patients are Asking, What You Need to Know”
Dr. Robert Saul

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Susceptible Periods for Epigenetic Changes throughout the lifespan

Gluckman et al., 2009
Let’s consider the case of “Henry”...

- A couple conceives via IVF after years of infertility treatments
  - G1P0 Mother age 38, thin (BMI 18), severe hyperemesis gravidarum in 1st trimester (BMI 17), smoked 3 ppd
  - Father age 42, BMI = 32 (obese)

- They choose preimplantation genetic diagnosis of fertilized embryos with array CGH

- Amniocentesis at 16 weeks EGA

- Family lives near a plastics manufacturing plant in North Carolina
This is Henry at Conception
Prenatal genetic studies

Array CGH:
arr cgh 122(3883BAC)x2, X(248BAC)x1,Y(65BAC)x1

Microarray analysis using a Cytochip whole genome 0.5Mb BAC array showed a normal hybridization pattern.

Amniocentesis:
Karyotype: 46,XY (450-500 bands)
Henry is born

- 41 wks GA, BW 4800 g, BL 54 cm, OFC 38 cm
- Apgars 7,8; hypoglycemia soon after birth: given IV fluids to resolve
- Physical exam:
  - Macrosomia
  - Macroglossia
  - Prominent nevus flammeus
  - Posterior helical pits
  - Large umbilical hernia

http://www.beckwith-wiedemann.info/
Henry in infancy

• Newborn Screening
  – North Carolina screens for 27 conditions on the Recommended Uniform Newborn Screening Panel (RUSP)
  – His initial screen for Cystic Fibrosis was positive by IRT
  – Reflexive DNA testing for 40 common CFTR mutations showed a single copy of ΔF508

• Henry gets sweat chloride testing:
  – Normal

• Genetic counseling: Likely carrier for CF
Genetics evaluation

- Overgrowth and congenital anomalies
- Tentative Diagnosis: Beckwith-Wiedemann syndrome
- Genetic testing for cause of BWS:
  - Methylation at chromosome 11p15
  - Loss of maternal methylation at IC2
- Why BWS??
  - May be related to IVF
  - Recurrence risks low
Genetics evaluation

• Dr. Saul takes a pedigree:

- ADHD
- 38
- 42
- 2 mos
- BWS
- CF carrier (ΔF508)
Beckwith-Wiedemann syndrome

• Clinical features:
  – Overgrowth
  – Omphalocele
  – Neonatal hypoglycemia
  – Renal abnormalities
  – Increased risk of embryonal tumors
  – Risk of hemihyperplasia

• Management—surveillance screening:
  – Quarterly abdominal U/S to age 8 years
  – AFP levels every 2 months to age 4
  – Annual renal U/S from age 8-mid-adolescence
Henry, age 2

- Lesion identified on right lobe of liver during routine ultrasound:
  - Hepatoblastoma, stage II
  - Elevated AFP
  - Treatment begun:
    - Surgical resection-complete
    - Chemotherapy

- Successful treatment—likely cure
Henry, age 10

- Still with overgrowth
- Prominent umbilical hernia largely resolved
- Has required surgical tongue reduction for improved speech articulation
- School: Diagnosed with ADHD
- Seen by PMD, treated with ritalin
- Why ADHD??
  - Hereditary factors (uncle with ADHD)
  - Prenatal exposures: maternal underweight, cigarettes
  - Possible BPA, phthalate exposures
Henry, age 25

- Graduated from college, marries his high school sweetheart
- Tries to start a family—no pregnancy after 1 year
- Workup for infertility:
  - Female evaluation: no obvious causes
  - “Male factor”: oligospermia, reduced sperm mobility and quality
- Referred to Genetics
Genetics evaluation

- Infertility and “history of BWS and cystic fibrosis”
- Dr. Saul updates the family history; reviews Henry’s medical history and lab reports from infancy
- He tests Henry’s wife for CFTR mutations to ascertain the risk of having a child affected with CF:
  - She has no mutations identified; therefore risk is low
- What about recurrence risk for BWS?
  - Since the imprint is reset in the germline, risk is low
- Why male factor infertility?
  - Unclear
  - Possible BPA, phthalate exposure from nearby plastics plant (endocrine disruptors)
  - Possible effects of chemotherapy for hepatoblastoma treatment
Henry, age 35

- He and his wife have 2 healthy children conceived by IVF-ICSI; no imprinting disorders
- Develops obesity, hypertension and type 2 diabetes
  - BMI 31 (obese)
- Why??
  - Diet
  - Sedentary lifestyle
  - Hereditary factors (dad with obesity)
  - Prenatal factors (mother’s extreme weight loss)
Henry, age 45

- Henry adopts a more active lifestyle, gives up junk food, and loses weight
- His diabetes is well-managed by an oral sulfonylurea medication
- His hypertension is managed with a β-blocker
- While mowing the lawn while wearing flip-flops, he suffers a bad foot laceration
- Treated with broad-spectrum antibiotics, including clindamycin
- Two weeks later, he develops crampy abdominal pain, fever and diarrhea:
  - Stool culture: positive for *C. difficile* toxin
  - Dx: Pseudomembranous colitis, possibly related to clindamycin
Henry, age 55

- Successful treatment of his colitis with oral vancomycin and probiotics to re-establish a healthy gut microbiome
- Develops fatigue, night sweats, and weight loss:
  - Blood test shows myeloid leukemic cells with blasts
  - Cytogenetic studies on blood reveal the Philadelphia chromosome (Ph)
- Dx: Chronic Myelogenous Leukemia
- Henry is treated with Imatinib
Ph: BCR-ABL fusion protein from t(9;22) in CML

Fusion protein is inappropriately activated
Treatment for CML targets the activated BCR-ABL fusion protein

STI-571 = Imatinib = Gleevec®

- Specific tyrosine kinase inhibitor
- 98% response in chronic phase
- 60-70% response in end-stage CML
After treatment with Imatinib

Normal 46,XY
No Ph

Quantitative PCR: undetectable BCR-ABL
Henry, age 65

- Treatment with Imatinib produced disease-free 10-year survival with full cytogenetic and molecular remission
- Henry enjoys his retirement years
Henry, age 75

- Develops intermittent atrial fibrillation
- His physician increases his β-blocker dose and wants to treat with warfarin to prevent stroke but is worried about hemorrhage
- Undergoes genetic testing for polymorphisms associated with warfarin metabolism in CYP2C9 and VKORC1 genes
- Using pharmacogenetic algorithms (www.WarfarinDosing.org), a starting dose is calculated to achieve INR 2-3
- Henry has resolution of symptoms
Henry, age 82

- Dies of “natural causes”
Putting it all together

• Beckwith-Wiedemann syndrome/hepatoblastoma:
  – Epigenetic disorder
  – Assisted reproductive technologies

• Cystic Fibrosis carrier:
  – Inherited mutation

• ADHD:
  – Maternal underweight
  – Maternal smoking
  – BPA/phthalate exposure
  – Genetic factors

• Infertility:
  – BPA/phthalate exposure
  – Hepatoblastoma chemotherapy
Putting it all together

• Obesity, HTN, diabetes:
  – Diet, lifestyle
  – Inherited factors
  – Prenatal contributors to obesity (maternal underweight)

• *C. difficile* colitis:
  – Drug exposure
  – Microbiome

• CML development:
  – Genetic factors
  – ? Prior treatment for cancer
  – ? Prenatal BPA/phthalate exposure

• Warfarin dosing:
  – Polymorphisms in drug metabolizing genes
Summary

• A complex interplay of genetic, epigenetic, environmental, and stochastic factors contribute to health and disease throughout the lifespan

• There are many opportunities for genetic testing and genetic counseling to be beneficial for an individual at different life stages
  – Not all require involvement of a genetics professional

• Some conditions have their origin in early life events (e.g., health of parents, prenatal exposures) and some can be traced to epigenetic processes
Questions?
Thank you for your participation!

For more information, please contact
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www.medicalhomeinfo.org/GPCI.aspx
Time Out for Genetics

Registration is now open for

“Epigenetics – What Your Patients are Asking, What You Need to Know”

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https://www2.gotomeeting.com/register/329126586