While genetics is certainly crucial to human development over a life cycle, epigenetics, environmental factors and random events are equally important, according to information presented during the webinar, “Genetics Across the Lifespan – Putting it All Together” held on November 29, 2012. The webinar, which featured Melissa Parisi, MD, PhD, FAAP, FACMG, was part of the Time Out for Genetics webinar series hosted by the Genetics in Primary Care Institute (GPCI).

Factors Affecting Human Development

DNA is only one part of human development. Other influences besides genetic material include the environment, random events and epigenetic factors, which are changes in gene expression that are not coded in the DNA sequence. All of these factors interact with each other to determine an individual's health. Even if two living beings have identical genetic material, they can have different phenotypes.

There are a number of stages throughout an individual's lifespan when genetic, epigenetic and environmental factors influence human development.

Much of this webinar focused on a case study about a fictional person named "Henry." This case study was created to illustrate how a multitude of genetic, epigenetic, environmental and random factors can affect a person’s health from preconception to death.
Preconception

- Henry was conceived via in vitro fertilization (IVF). Prior to implantation, his parents chose to have their fertilized embryos tested for many genetic conditions using array comparative genomic hybridization. The results were normal.
- Henry’s mother was thin and lost a lot of weight during the first trimester of the pregnancy due to severe vomiting. She also smoked three packs of cigarettes per day during the pregnancy. Henry's dad was obese. In addition, they lived near a plastics manufacturing plant.
- Henry’s mother underwent amniocentesis for karyotype testing when she was 16 weeks pregnant. The results were normal.

Birth

- Henry was born at 41 weeks gestational age, weighing 4800 grams and measuring 54 centimeters in length and 38 centimeters in head circumference, all large for gestational age.
- Shortly after birth, he had apgar scores of 7 and 8, and he was hypoglycemic.
- A physical examination of Henry revealed macrosomia, macroglossia, prominent nevus flammeus, posterior helical pits and a large umbilical hernia.
- Henry’s initial newborn screening test was positive for cystic fibrosis.
- Reflexive screening for 40 common mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene showed a single copy of ∆F508, the most commonly occurring mutation of CFTR.
- Henry then underwent sweat chloride testing but the test results came back normal, indicating that Henry was probably a carrier of the cystic fibrosis gene but not affected with cystic fibrosis. It is likely that the cystic fibrosis carrier gene was an inherited mutation passed through generations of his family.
- Henry was referred for genetic counseling.

Genetics Evaluation

- At Henry’s genetics evaluation, he was tentatively diagnosed with Beckwith-Wiedemann syndrome (BWS), an epigenetic disorder, because of his overgrowth and congenital anomalies.
- To confirm BWS and determine the cause, genetic testing was performed to look for methylation at chromosome 11p15, and a loss of maternal methylation at imprinting center 2 was discovered. This is found in about half of all children diagnosed with BWS.
- Because the parents had undergone selective IVF and an amniocentesis during the pregnancy, both resulting in normal tests, they were confused as to why Henry would be born with this condition.
- The geneticist reassured them that Henry’s BWS was attributable to an imprinting defect that is extremely difficult to detect prenatally.
- The geneticist indicated that BWS may be associated with IVF but that the risk of recurrence was low because there was no family history of this condition.

Henry, Age 2

- During a routine ultrasound, a lesion was detected on the right lobe of Henry’s liver. It was biopsied and found to be hepatoblastoma, stage 2. He also had elevated alpha–fetoprotein levels in his blood.
- The lesion was biopsied and found to be focal without significant spread.
- Henry underwent chemotherapy, which was successful.

Henry, Age 10

- Henry still had some overgrowth, but his other issues at birth had resolved.
- He was diagnosed with attention deficit hyperactivity disorder (ADHD) and prescribed Ritalin.
- His ADHD was likely multifactorial in origin but might be attributable to an uncle with ADHD, prenatal exposure to maternal underweight and cigarettes, and possible exposure to BPA and phthalates from the plastics manufacturing facility located near his home, each of which could have increased Henry’s risk of developing ADHD.
Henry, Age 25

- Henry and his new wife tried to become pregnant unsuccessfully for more than one year.
- They visited an infertility specialist to determine why they were having difficulty conceiving.
- The test results indicated that Henry’s wife had no obvious causes for the infertility but that Henry had low sperm count, mobility and quality.
- They were referred to a genetics specialist because of the fertility issues and Henry’s history of BWS and cystic fibrosis carrier status.

Genetics Evaluation

- Henry’s wife was tested for CFTR mutations. The test result was negative.
- Henry and his wife were reassured that the risk of any child of theirs having BWS would be low since the imprint is reset in the germ line.
- Henry was told that his sperm issues could be due to exposure to BPA and phthalates from the plastics manufacturing facility near his childhood home or from the chemotherapy he received as a child for his liver cancer.
- Eventually, Henry and his wife conceived two healthy children using IVF—intracytoplasmic sperm injection. Neither child was born with an imprinting disorder.

Henry, Age 35

- Henry was obese with hypertension and type 2 diabetes.
- His issues were likely due to a sedentary lifestyle, hereditary factors related to his father’s obesity, and prenatal factors related to his mother’s extreme weight loss during her pregnancy, which predisposes the infant to weight gain, obesity, hypertension and cardiovascular disease later in life.

Henry, Age 45

- Henry adopted a better diet and more active, healthy lifestyle. With these changes and medications, he was able to lose weight and manage his diabetes and hypertension from 10 years earlier.
- While mowing the grass, Henry suffered a severe foot laceration and was treated with broad-spectrum antibiotics, including clindamycin, to prevent anaerobic infection and diabetic foot ulcers.
- Soon after, Henry began to experience cramping abdominal pain, fever and diarrhea. A stool culture tested positive for C. difficile toxin and he was diagnosed with pseudomembranous colitis, possibly as a result of the clindamycin.
- Henry’s colitis was successfully treated with oral vancomycin and probiotics to reestablish a healthy gut microbiome.

Henry, Age 55

- Henry was diagnosed with chronic myelogenous leukemia after a blood test showed myeloid leukemic cells with blasts and a cytogenetic study showed the Philadelphia chromosome, which encodes an activated fusion protein.
- He was treated with Imatinib, a very specific inhibitor of the cancer-causing fusion protein, which eventually put him into remission.

Henry, Age 75

- Henry developed intermittent atrial fibrillation and was prescribed a beta blocker.
- Henry underwent genetic testing for polymorphisms associated with warfarin metabolism in the CYP2C9 and VKORC1 genes to ensure that warfarin would not cause Henry to hemorrhage.
- Using a pharmacogenetic algorithm, Henry’s physician was able to calculate the appropriate dosage of warfarin for Henry to reduce his risk of stroke.
- His symptoms were resolved, and he died of natural causes at age 82.

About the Presenter

Dr Parisi is a clinical geneticist and chief of the Intellectual and Developmental Disabilities Branch of the National Institute of Child Health and Human Development, National Institutes of Health. Dr Parisi also is a member of the GPCI Project Advisory Committee and a member of the American Academy of Pediatrics (AAP) Committee on Genetics.

About GPCI

The GPCI was established to increase primary care providers’ knowledge and skills in the provision of genetic-based services. The GPCI is a cooperative agreement between the US Department of Health and Human Services, the Health Resources & Services Administration, the Maternal & Child Health Bureau and the American Academy of Pediatrics.

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