Perinatal Care Matters

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Waking Up from the Diabetes Genetics Nightmare

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Dr. James V. Neel, the father of human genetics, wrote a chapter entitled "Diabetes Mellitus – A Geneticist's Nightmare" in 1976 (1). At that time, little was known about diabetes genes; the first successful identification of a disease gene using the positional cloning approach, the gene for cystic fibrosis, would not occur for another 13 years (2,3). However, the possibility of genetics playing a role in diabetes risk was generally known. People would talk about diabetes "running" in their families, which was essentially describing the passing of diabetes genes from one generation to another. However, what those genes were and how they worked to confer risk were mysteries and Dr. Neel's chapter served as a warning of the challenges that lay ahead.

The benefits of identifying diabetes genes seemed tremendous. The discovery of these genes would allow: accurate prediction of who might develop diabetes, creation of therapies tailored to each individual, identification of new drug targets, and maybe development of gene therapies to correct the genetic defect(s) and cure the disease. Between 1976 and 2006, tremendous effort was expended to identify diabetes genes. There were success stories, like the identification of peroxisome proliferator-activated receptor (*PPARG*) as a diabetes gene, but in general Dr. Neel's predictions rang true. The reality was that the individual effect of diabetes genes was small and the technology and methods of the 1980s and '90s were not powerful enough to detect these effects.

However, conditions changed rapidly as we entered the new millennium. The Human Genome Project (http://genome.ucsc.edu), an effort to decode our DNA, completed a first draft of the human genome in 2000 (4). The HapMap Project (http://www.hapmap.org), an effort to identify genetic difference across human populations, was initiated and has identified over six million differences across the human genome to date (5,6). Finally, improvements in technology now allow scientists to measure hundreds of thousands of genetic differences across the human genome in several thousand individuals in the span of weeks, whereas such a feat was deemed impossible a mere decade ago.

These breakthroughs, coupled with improved study designs and statistical methods, have led to a new era in human genetics. Prior to 2006, only two genes for type 2 diabetes had been identified and universally accepted by the scientific community. In 2006, DeCode Genetics, a private venture studying the population of Iceland to identify genes for a variety of diseases, reported the identification of transcription factor 7-like 2 (*TCF7L2*) as a susceptibility gene for type 2 diabetes (7). Then, in the first six months of 2007 seven new genes for type 2 diabetes were reported by five independent research groups (8-12). What was important about these recent findings was the significant overlap in results across the studies and that many of the genes had hypothesized effects on the pancreatic β-cell. Four more genes will appear in the literature by the time this article is published. However, individually each of these genes only raised the odds for diabetes by 5-10% and together they accounted for only a small fraction of diabetes cases. The specter of Dr. Neel's diabetes nightmare seemed to rise again.

So far, our knowledge of these ten diabetes genes has not allowed us to predict diabetes, strongly suggesting that the identification of genes is merely the first step. We still need to understand how these genes work to increase risk for diabetes and if they also confer risk for gestational diabetes mellitus (GDM). This has been the focus of our research at the Keck School of Medicine of University of Southern California (USC). Previous research by Dr. Thomas Buchanan of our institution showed that Latinas diagnosed with GDM are at elevated risk for type 2 diabetes (13-15); an observation that has been extended to other ethnic/racial groups (16). In his studies, over half these women developed type 2 diabetes within five years after delivery (13), and their risk increased with each subsequent pregnancy (14). His research also noted these Latinas did not appropriately increase their insulin secretion compensate for insulin resistance in peripheral tissues (15,17), but their risk for type 2 diabetes could be significantly reduced by reducing insulin secretory demand by treating them with a thiazolidinedione (18,19).

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Diabetes Genetics con't….

Given these observations, five years ago we initiated the BetaGene Study with the goal of identifying genes underlying this inability to secrete insulin and to understand how those genes worked to increase risk for type 2 diabetes. We are collecting data on families of a Latina with a previous diagnosis of GDM, collecting their DNA, measuring their body fat, and doing detailed metabolic measurements. To date, we have studied over 2,500 individuals in over 200 families. We have begun to investigate whether the genes identified for type 2 diabetes are also associated with GDM and the specific measurements from our BetaGene participants. More importantly, we are also studying whether the effect of these genes is altered by other factors like body fat, diet, or physical activity. For example, we recently showed that the effect of *TCF7L2* on insulin secretion differed by the amount of body fat (20). This observation is important, because it is generally known that a 7-10% loss of body weight can reduce type 2 diabetes risk by an average of ~50%. However, individual risk reduction with weight loss may depend upon the specific genes, like *TCF7L2*, that interact with body fat. Efforts like the BetaGene study should provide new insights into how these diabetes genes interact among themselves and with environmental factors to alter biology and increase risk for diabetes, one of the complicating factors noted in Dr. Neel's nightmare scenario.

It has been thirty years since Dr. Neel warned us of the "geneticist's nightmare". Dr. Neel recognized the challenge in identifying diabetes genes, even in the age where the genes were unknown. But with the identification of type 2 diabetes genes and the likely discovery of additional genes in the near future, we are just now starting to awaken from Dr. Neel's "nightmare". The next few years should begin to see translation of some of the promises of genetic research into diabetes treatment and prevention.

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Birth Certificates Matter

Everyone knows that gathering information to complete birth certificates can be a time consuming and sometimes difficult task in a busy hospital obstetrics department. The accuracy and completeness of the birth certificate is critical in gathering information that provides statewide, regional and hospital specific data for the entire State of California. Many medical providers and researchers use this information to drive quality improvement activities so the accuracy and completeness of these statistics is vital.

In recognition of the complexity of gathering and processing the information needed for the birth certificate, the State Office of Vital Records has scheduled ***Birth Data Quality Workshops*** throughout the state in 2008 as follows:

- Alameda County- March 13, 2008;
- San Diego- April 9, 2008;
- Fresno- May 15, 2008;
- Sacramento- June 4, 2008;
- Long Beach- July 10, 2008;
- Pasadena-August 20, 2008;
- San Bernardino- September 18, 2008; and
- Ventura- October 8, 2008.

The agenda for these workshops will focus on reducing the number of unknowns and/or missing data items. There may be sharing of best practices amongst attendees and awards given to those with the best or most improved data quality.

As a reminder, Alan Oppenheim, from the State Office Center of Health Statistics, has stated that one of the areas that have the most incomplete data is the last menstrual period (LMP) (field 25A). This field requires month, day and year. Many times the patient or prenatal record may not have these dates, however if a birth clerk is trained and has access to a pregnancy wheel, that may allow the LMP to be calculated so that the whole date can be filled in. Proofreading a birth certificate before mailing it may prevent delay in registration. A correct and complete certificate will ensure accurate data and it is well to remember this document follows the child all of his or her life.

Kathy Bird, Nurse Educator, Region 7, RPPC

California OB Quality Improvement: A CMQCC Update

The California Maternal Quality Care Collaborative (CMQCC) is a state-wide initiative with many stakeholders. CMQCC's objectives are to:

- Develop a statewide effort for collaborative maternal quality improvement;
- Implement data-driven quality improvement;
- Develop and refine quality measures; and
- Examine approaches to reduce disparities in outcomes.

A major goal of CMQCC is to reduce maternal mortality and morbidity in California. In order to make improvements to such a broad and complex issue there is a need to engage as many partners as possible. One group that clinicians have not worked much with but who have a lot of potential impact on Obstetric outcomes are the local health departments. One of CMQCC's initiatives for this coming year is to work with Local Health Jurisdictions (City and County Departments of Public Health) to brainstorm on ways they might be helpful in partnering with clinicians to reduce maternal mortality and morbidity. We anticipate that the State Department of Public Health will fund 4 or more pilot projects from among the 18 local health jurisdictions who have decided to submit proposals. Stay tuned!

CMQCC is establishing several committees to work on quality improvement methods and tools, data analysis, communications, relationships with companion organizations, and governance.

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Galactosemia: In Review

Galactose is a carbohydrate found primarily in human and bovine milk, and milk products. When the di-saccharide, lactose hydrolyzes it forms glucose and galactose by the intestinal enzyme, lactase. Galactose is then further metabolized to form glucose[1]. Galactosemia is an autosomal recessive metabolic disorder. Individuals with the condition lack a transferase enzyme needed to convert galactose to glucose. As a result individuals have impaired galactose metabolism. Galactosemia occurs at a rate of 1 in 73,000 births in the state of California[2].

Over a 150 galactosemic mutations have been noted and 3 primary variant phenotypes distinguished. These include a complete or total transferase deficiency, known as ***Galactose-1 phosphate uridyl transferase*** **(GALT)** deficiency; partial GALT variants include the Duarte gene consisting of partial enzyme activity; ***Galactokinase*** **(GALK)** deficiency, and ***Uridine diphosphate galactose 4-epimerase*** **(GALE)** deficiency[3].

GALT

GALT is a complete transferase enzyme deficiency commonly known as "Classical Galactosemia," it is the most common and most severe form of the disease. Symptoms usually present within the a few days of life, after the initiation of breast milk or milk-based formulas. Untreated or unidentified infants with GALT may present with different frequencies as in liver dysfunction, renal dysfunction, cataracts, abnormal neurodevelopment or premature ovarian failure [4, 5].

Neonatal manifestations of GALT include: Jaundice (74 %), Vomiting (47 %), Hepatomegaly (43%), Failure to thrive (29%), Poor Feeding (23 %), Lethargy (16 %), Diarrhea (12 %), Sepsis (10 %) with Escherichia coli occurring in 76% of septic cases [4,5,].

Laboratory findings associated with GALT include: increased plasma galactose levels, increased erythrocytic galactose-1 P concentration, increased galactitol levels in blood and urine. Abnormal liver functioning tests, include conjugated or unconjugated hyperbilirubinemia, coagulopathy, increased plasma amino acids, galactosuria, glucosuria, aminoaciduria, albuminuria, metabolic acidosis, and hemolytic anemia [6].

Partial GALT variants occur with the Durate gene and can result in various levels of GALT enzyme activity. Individuals with over a 50% GALT activity may have little evidence of abnormality during the neonatal period or even throughout their life time [7].

GALK

Galactokinase (GALK) deficiency occurs with the inability to convert galactose to galactose-1-P. Infants with GALK can present with bilateral cataracts[8]. Diet therapy can assist in resolving the cataracts. Diagnostic confirmation is preformed by utilizing an assay of GALK activity in erythrocytes.

GALE

Uridine diphosphate galactose 4-epimerase (GALE) deficiency occurs with the inability to convert UDP galactose to UDPglucose. This type of defect is typically localized within erythrocytes. Growth and development for individuals with GALE is typically normal [9]. Diagnostic confirmation is preformed by utilizing an assay of GALK activity in erythrocytes.

Newborn Screening Program

California Newborn Screening Program (NBS) routinely tests for GALT. When initial screen is positive, recall specimens are collected to confirm results and to assess for specific mutations like Partial GALT, GALE and GALK. Current recall testing and confirmatory site is located at Children's Hospital, Los Angeles[10].

Key NBS Points to Note

False negative GALT is a concern for infants maintained on lactose-free diets or lactose restricted formula, and neonates who have received blood transfusion prior to the NBS collection. False negative testing can be omitted with careful planning. If a RBC transfusion is anticipated prior to 12 hours of age, NBS blood specimen collection should occur prior to the transfusion. Additional blood collection will be needed 24 hours after the last RBC transfusion and at 6 days of age. Cord blood can also be utilized and submitted as a pre-transfusion specimen. Together proper collection of the pre-transfusion and post-transfusion specimens will allow for appropriate analysis; however Infants with a history of intrauterine blood transfusions will need both NBS and hemoglobin DNA testing of whole blood[11].

Newborns have also presented with mildly elevated galactose findings resulting in false positive results; stemming from other conditions: liver dysfunction stemming from porto-system vascular shunts, biliary atresia, and Fanconi-Bickel syndrome [12, 13, 14].

Thus, acting upon clinical findings in light of negative new born screening analysis is of essential importance. Inadequate results should prompt additional testing specimens from physician to Newborn and Prenatal Screening Laboratory (NAPS) for additional analysis[15].

Treatment

Infants with clinical symptoms, pending recall results, or with a Galactosemia diagnosis, need to be placed on a lactose-free diet. The use of lactose-free formulas like soy based formulas, provide safe, appropriate and recommended nutrition for newborns with Galactosemia [3]. Removal of galactose from diet will assist in resolving many of the early symptoms, including cataracts [4,5].

Supportive Information

Two educational tools are readily available from DHS on-line: "Parents' Guide to Galactosemia," Part 1 written for the first 6 months of a newborn's life and, "Parents' Guide to Galactosemia," Part 2 designed for solid food introductions and beyond. Each guide assists caregivers with specific information regarding frequently asked questions, hereditary information, infant growth, development, treatment, and contact support information. Since the primary intervention

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for infants with Galactosemia is a lactose-free diet, the booklets teach practical methods for reading food labels, looking for hidden forms of lactose such as fillers in medications and vitamins, and assisting parents with what to expect as their child grows. Newborns with Galactosemia are assisted by a referral to California Children's Services. A physician specializing in metabolic conditions will assist in the care and follow-up[16].

Long Term Care

Vigilant health care support and monitoring of children with Galactosemia is of the essence. Even with a lactose-free diet, endogenous galactose synthesis occurs; and metabolites remain within the blood and urine. Individuals with Galactosemia may later develop complications in speech, language difficulties, ovarian failure, cataracts, or be affected with focal neurological conditions as adolescents or young adults[17].

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Written by: Katina Kraniak, RN, PHN, Region 6.1

Folic Acid May Help Prevent Premature Birth

In a large study that included almost 40,000 women, a team of U.S. and Irish researchers found that women who took folic acid supplements for a year or longer before conception had a 70 percent decreased risk of preterm birth between 20 and 28 weeks of gestation. "There have been all sorts of protocols, lifestyle interventions and medications tested, and nothing has made a difference in preterm births, so this is a really exciting study," said Dr. Katharine Wenstrom, president of the Society of Maternal-Fetal Medicine, and a professor of obstetrics and gynecology at Vanderbilt University Medical Center in Nashville.

Dr. Wenstrom said it's likely that folic acid is regulating certain genes that malfunction to cause early labor. "Now that we know that folic acid makes a huge difference, researchers can look at the different reactions that folic acid causes and see which might be related to preterm labor".

A premature birth is one that occurs before 37 weeks' gestation, according to the U.S. National Institutes of Health (NIH). Improved medical knowledge and technology have made survival for these small infants more likely -- of babies born at 28 weeks or after, 90 percent are expected to survive, according to the NIH. But the earlier a baby is delivered, the greater the risk of serious complications, including bleeding in the brain, infection, delayed growth and intestinal problems, according to the NIH.

The new study included 38,033 women pregnant with one baby. Women who had known pregnancy complications, such as preeclampsia or high blood pressure, and women pregnant with babies with known chromosomal or other birth defects weren't included in the study. A baby's gestational age was determined by ultrasound between 10 and 14 weeks of pregnancy. Folic acid supplementation history was reported to the researchers by the women.

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The researchers found that women who took a folic acid supplement for at least a year prior to becoming pregnant reduced their risk of preterm delivery between 20 and 28 weeks of gestation by 70 percent. A year of folic acid supplementation dropped the risk of delivering during weeks 28 through 32 by 50 percent, according to the study. "This study saw a huge decrease in spontaneous preterm delivery for women who took folic acid for one year prior to conception. Now we can add prevention of prematurity to the mix of reasons for all women to take an additional folic acid supplement," said Dr. Alan Fleischman, senior vice president and medical director of the March of Dimes.

Results of the study were to be presented Thursday at the Society for Maternal-Fetal Medicine annual meeting, in Dallas. Fleischman noted that the current findings are preliminary and need to be published in a peer-reviewed medical journal. In the meantime, Wenstrom said she believes that everyone -- both male and female -- should take a daily folic acid supplement in addition to a multivitamin containing folic acid.

"Cereal and grain products are fortified with folic acid, but the level of fortification isn't optimal. Folic acid influences so many things. It reduces the risk of stroke, cardiovascular disease, and it prevents birth defects," she said. "It's a simple preventive measure for a variety of severe problems."

The March of Dimes recommends that women take 400 micrograms daily of folic acid before becoming pregnant, and continuing to take folic acid throughout the pregnancy.

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Public Policy & Legislation

With an exciting year of ground-breaking presidential elections ahead, we must not forget to focus equal attention on California state legislation as well. On January 10th, Governor Schwarzenegger declared a state of fiscal emergency which called Legislature into a special session to address a projected budget gap of $14.5 billion through June 2009. This state of fiscal emergency requires Legislature to send proposed legislation addressing this fiscal emergency to the governor within 45 days of the declaration. If Legislature fails to send the governor bills to address this deficit within this specified period, they may not act on any other bills until legislation is passed.

In response to the projected budget gap, the governor has proposed a 10 percent across-the-board spending reduction for nearly every General Fund Program. Health and Human Services would take a significant hit shouldering 83.5% of the 2007-2008 proposed reductions and 29.5% of the 2008-2009 reductions. A large majority of these reductions would effect the Department of Health Care Services (DHCS), The Department of Public Health (DPH), The Department of Mental Health and The Healthy Families Program. To read the full budget summary, please visit www.ebudget.ca.gov.

Below is a brief summary of legislation to keep an eye on in 2008. This year is the second year of a two year cycle. As many of the proposed bills in 2007 became law in January, new bills are being introduced while a number of old bills are up for reconsideration. For more information on the status of specific bills, please visit www.leginfo.ca.gov.

California Assembly Initiatives

AB 1: Laird and Dymally - Health Care Coverage

This bill would expand eligibility for the Medi-Cal program and the Healthy Families Program by allowing children with family incomes at or below 300% of the federal poverty level to qualify for the program and would delete the specified citizenship and immigration status requirements.

AB 30: Evans - Inborn Errors of Metabolism

This bill would require health plans to cover the cost of treatment, including formula and food, for children with metabolic disorders. Coverage is not required except to the extent that the cost of the necessary formulas and special food products exceeds the cost of a normal diet.

AB 1275: DeSaulnier - Domestic Violence, Child Abuse

This bill authorizes a county board of supervisors, upon making findings and declarations supporting the need for governmental oversight and coordination of the multiple agencies dealing with domestic violence and child abuse, to authorize an increase in the fees for certified copies of marriage certificates, birth certificates, fetal death records, and death records, for the purpose of funding governmental oversight and coordination of domestic violence and child abuse prevention and to submit a related report.

AB 1472: Leno –Healthy Places Act of 2008

This bill establishes the California Healthy Places Act of 2008. It requires various state agencies and departments to collaboratively support childhood development, prevent injury, illness, and chronic disease, ensure environmental health, and reduce health disparities by providing knowledge, guidance and resources for public health assessments of land use and transportation system planning. It provides funding, technical assistance and training to eligible local entities to prepare health impact assessments.

AB 1511: Leno – Stronger Families for California Act

This bill would establish the Stronger Families for California Program, a continuing information and public education program, within the Department of Health Services, with the primary goal of decreasing teenage pregnancies and sexually transmitted diseases through a continuing information and public education program that equips parenting adults with the communication skills necessary to talk with their children about sex, sexual health, and making well-informed decisions to protect their health and safety.

AB 1605: Lieber - DPH: Public Health Nurse

This bill requires the Director of the State Department of Public Health to appoint one of the chief deputies as the State Public Health Nurse, to act as a liaison to public health nursing agencies in addition to other duties.

California Senate Initiatives

SB 840: Keuhl - Single-Payer Health Care Coverage

This bill would establish the California Healthcare System and make all California residents, including those who travel out of state, eligible for specified health care benefits. The California Healthcare System would, on a single-payer basis, negotiate for or set fees for health care services provided through the system and pay claims for those services. The bill would create the Office of Health Planning to plan for the health care needs of the population, and the Office of Health Care Quality to support the delivery of high quality care and promote provider and patient satisfaction.

SB 179: Ashburn – CalWORKS Reporting Requirements

Current law requires the county to implement a recipient monthly reporting system where the county would redetermine recipient eligibility and grant amounts on a quarterly system. This bill would repeal the requirements relating to quarterly redetermination and prospective determination grant amounts, and would impose similar requirements for a semiannual redetermination, to take effect January 1, 2009.

SB 164: Migden – Prenatal Screening

This bill changes the name of the Birth Defects Monitoring Program to the Birth Defects Monitoring and Biomedical Resources Program. It would require the DPH to charge investigators who are approved by the department to use pregnancy blood for research purposes, a fee for costs related to data linkage, storage, retrieval, processing, data entry, reinventory, and shipping of newborn blood samples or their components, and related data management. It protects identifying information. This bill requires billing of specified entities to cover the costs of confidentiality protection.

SB 468: Padilla – Shaken Baby Syndrome

This bill relates to shaken baby syndrome. It revises legislative findings and declarations to state that programs focusing on providing information on shaken baby syndrome by educating adults about the dangers of shaking a child and ways to avoid that conduct have been effective in reducing the number of deaths from shaken baby syndrome. This bill requires the Department of Social Services to establish the voluntary Shaken Baby Syndrome Education Pilot Program. This bill would provide that its activities would be funded exclusively with funds allocated to the department from the State Children's Trust Fund.

SB 825: Padilla – Public Health: Shaken Baby Syndrome

This bill establishes the Shaken Baby Syndrome Education Program. It requires the DPH to select programs from eligible counties which are designed to provide new parents and other caregivers of newborns and infants with information and education relating to the prevention of shaken baby syndrome. It requires a report on the effectiveness of the program in reducing the number of injuries and deaths. This bill provides that the funding will be from the Children's Trust Fund.

For a detailed summary of these bills and other legislation, visit http://www.paclac.org/policy/policyLegislative.htm
Submitted by Lisa Pettinato, PAC/LAC Region 6.3-6.6

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