

Opportunities for primary care research in rare disorders: my experience with the Plain communities



Welcome



James DeLine, MD
La Farge Medical Clinic
Center for Special Children



Center for Special Children
A program of Vernon Memorial Healthcare

Objectives



- Introduction to Plain community
- Birthing Center
- Collaboration – University of WI-Madison & others
- Genetic Disorders
- Research Efforts

La Farge Medical Clinic

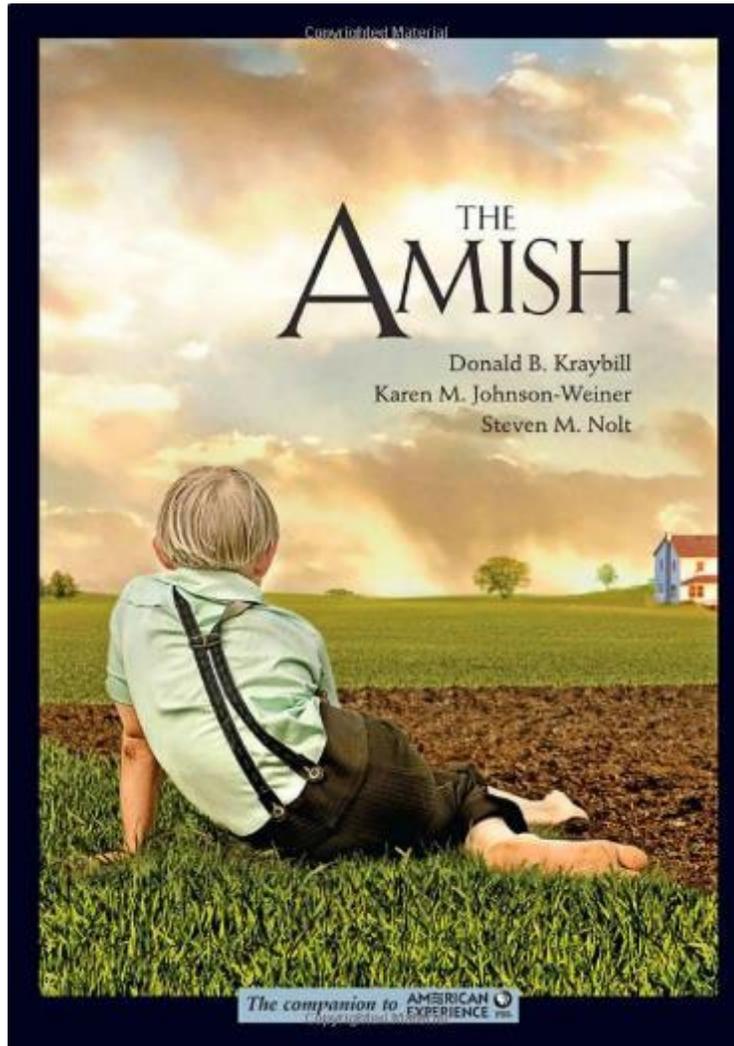


- 1983: Private solo practice
- 1995: Birthing Center opened
- 2004: LFMC joined Vernon Memorial Healthcare
- 2012: Genetics in Amish presentation by Dr. Holmes Morton
- 2015: Center for Special Children established

The Amish



- “Plain” in dress; horse & buggy
- No electricity or indoor plumbing
- School through 8th grade
- Religion is center of life
- Western medicine not first choice



Plain Talk about Providing Health Care to Plain Communities

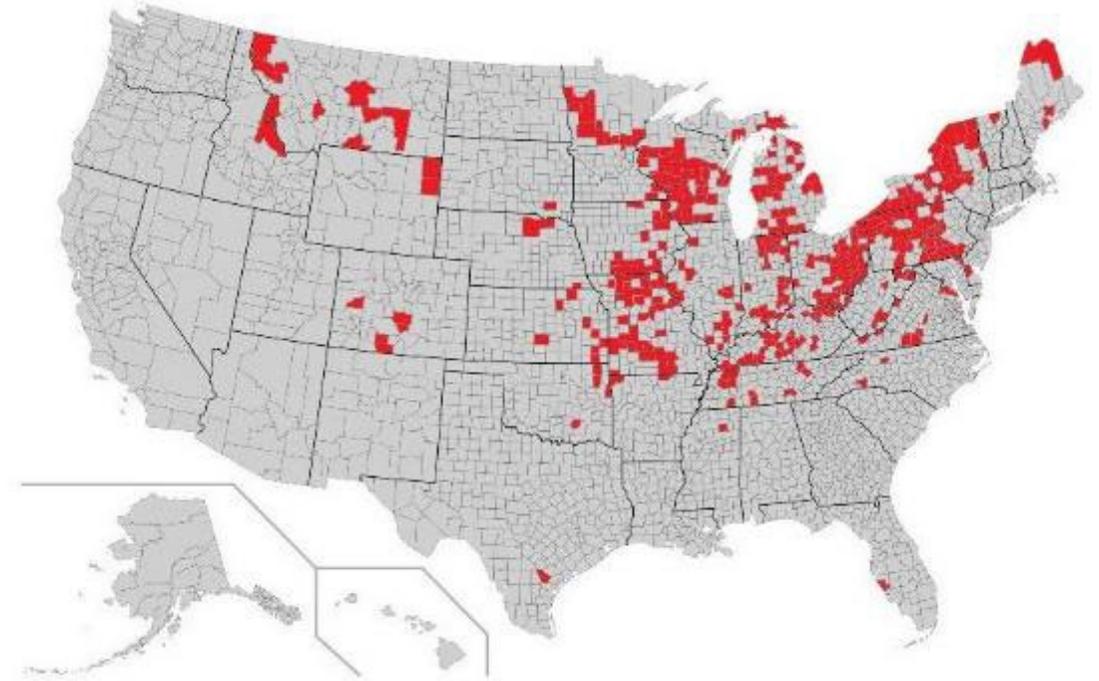
I. Introduction

As their numbers grow in Wisconsin signs of Plain Amish and Mennonite communities are becoming more familiar. Horse-drawn buggies, woodworking shops, greenhouses, bakeries, bulk food stores, along with other Amish and Mennonite businesses are more common. Because of this increasing familiarity, we may feel we know or understand this culture. However, familiarity must not be confused with understanding, especially as we strive to provide effective and economical health care to this unique cultural group in our midst. Understanding the history of the Plain movement, the organization of contemporary communities, and the variations among the different groups that have settled in Wisconsin can give health care providers a foundation for the lifelong process of learning to provide respectful and appropriate health care to this population.

The Amish, Old Order Mennonites, and German Baptists are among the groups in Wisconsin that identify as Plain communities. These groups share a history that can be traced to the Anabaptist movement, which began in 1525 in Switzerland at the time of the Protestant Reformation. The Mennonites were established in the mid 1500's. The Amish separated from the Mennonites in 1693 following their leader Jacob Ammann. Both of these groups experienced religious persecution in Europe and migrated to North America beginning in the first half the eighteenth century. Since that time many offshoots of these groups have formed usually because of differences of opinion over how to apply their shared faith to everyday life. Members of these groups have continued to dress simply with subtle, but significant differences in clothing style between the groups such as sleeve length, clothing fasteners, and color of fabric. In general, Mennonites represent a diverse group and most do not wear plain dress. The Old Order Mennonite communities wear plain dress. For the purposes of this guide, members of Amish, Old Order Mennonite, and other Plain communities who wear plain dress and live according to their Christian faith will collectively be referred to as Plain people.

Amish History

- Left Europe to escape religious persecution
- First migration to mid 1700s primarily to Pennsylvania
- Second migration mid 1800s primarily to Ohio
- Current population: 375,000



Birthing in Plain communities



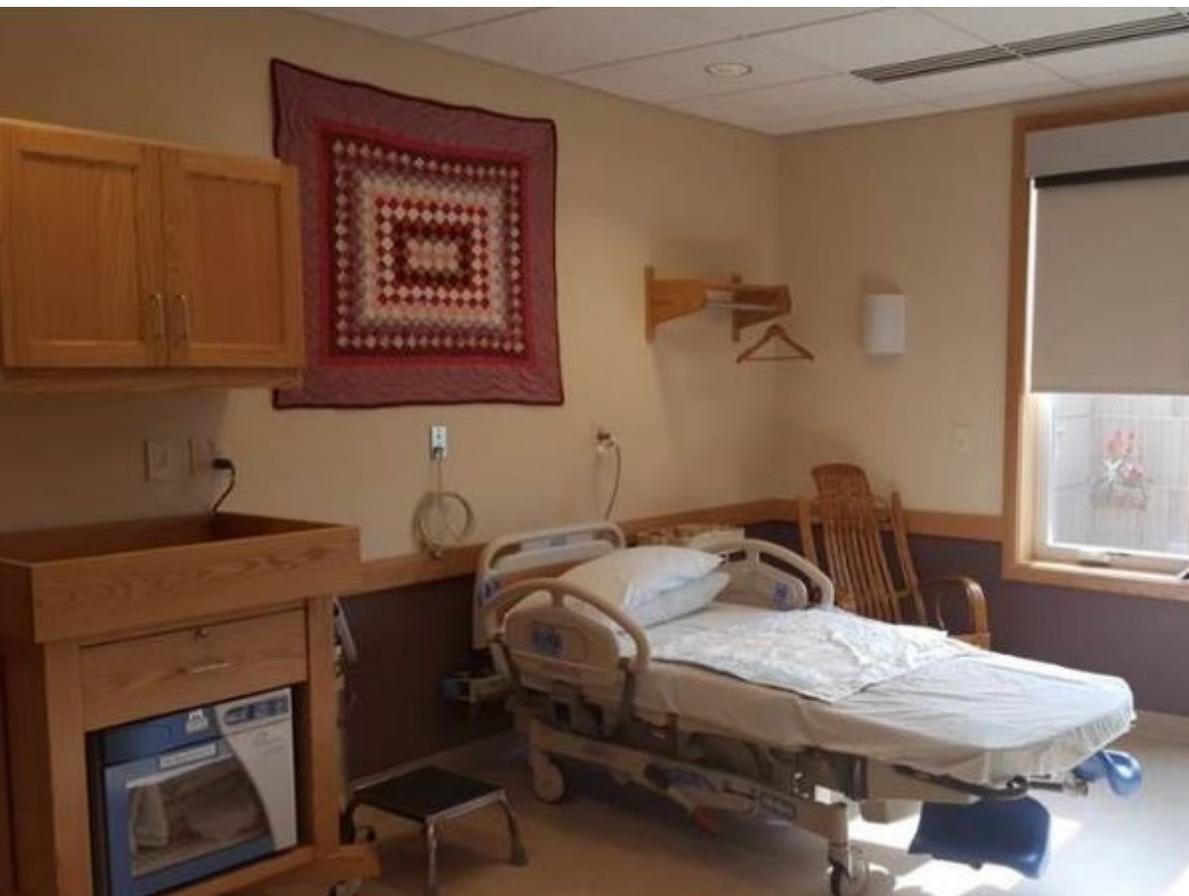
- Pregnancy through reproductive years
- Large family size (average of 7 children)
- Home births: Lay Amish birth attendants or licensed/certified midwifery
- Medical issues common: HTN, obesity, inherited disorders, etc.
- OB complications: twins; malpresentations; PPH; Rh disease

Birthing Center



Birthing center opened in 1995

- >2,000 deliveries
- C-section rate of 4%
- 95% successful VBAC



Low Primary Cesarean Rate and High VBAC Rate With Good Outcomes in an Amish Birthing Center

James Deline, MD¹

*Lisa Varnes-Epstein, MHS, PA-C,
CPM¹*

Lee T. Dresang, MD²

Mark Gideonsen, MD²

Laura Lynch²

John J. Frey III, MD²

¹Amish Birthing Center, La Farge,
Wisconsin

²University of Wisconsin School of
Medicine and Public Health, Madison,
Wisconsin

ABSTRACT

PURPOSE Recent national guidelines encourage a trial of labor after cesarean (TOLAC) as a means of increasing vaginal births after cesarean (VBACs) and decreasing the high US cesarean birth rate and its consequences (2010 National Institute of Health Consensus Statement and American College of Obstetricians and Gynecologists revised guideline). A birthing center serving Amish women in Southwestern Wisconsin offered an opportunity to look at the effects of local culture and practices that support vaginal birth and TOLAC. This study describes childbirth and perinatal outcomes during a 17-year period in LaFarge, Wisconsin.

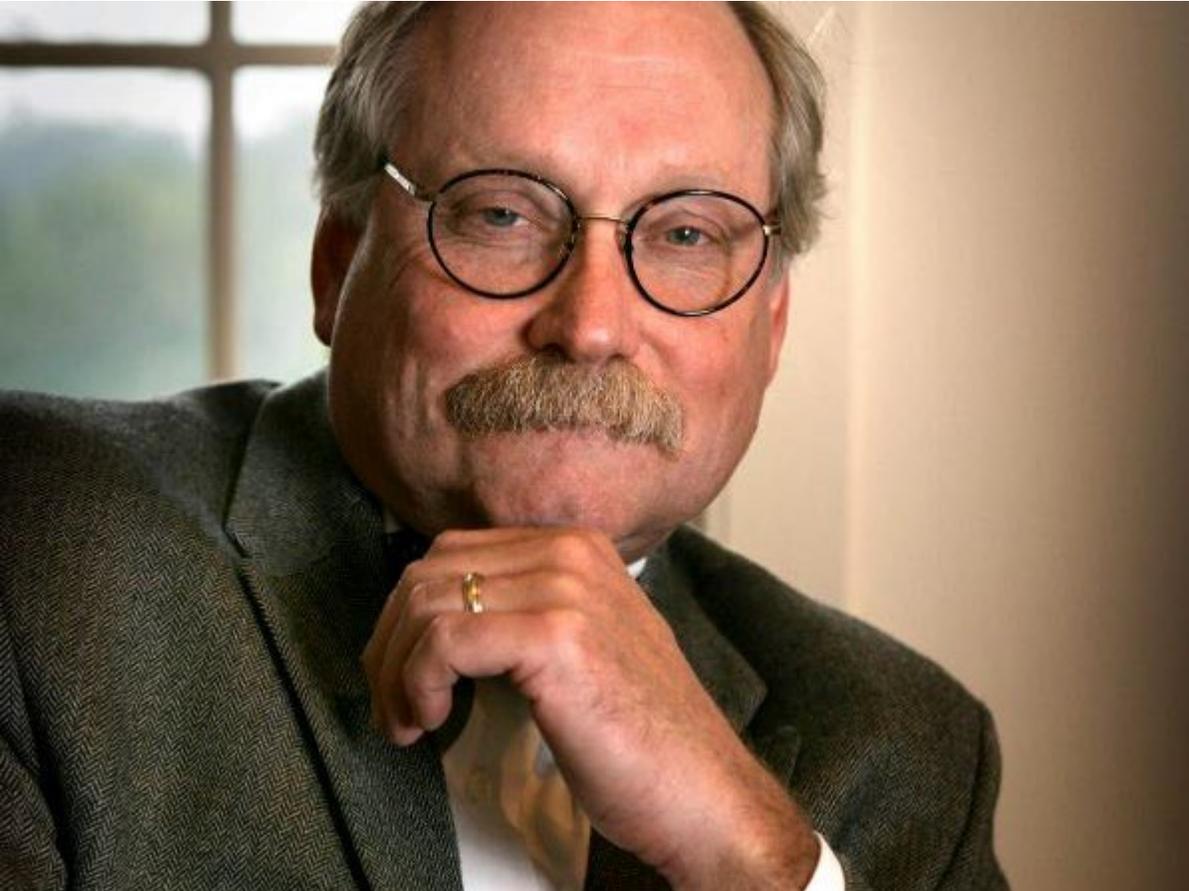
METHODS We undertook a retrospective analysis of the records of all women admitted to the birth center in labor. Main outcome measures include rates of cesarean deliveries, TOLAC and VBAC deliveries, and perinatal outcomes for 927 deliveries between 1993 and 2010.

Collaboration



- 2010: Critically ill Amish infant w/ SCID transplanted against parent's wishes
 - Mistrust of UW & medical establishment
- Quarterly round tables with UW-Madison, MDs, RNs, Midwives, Amish and Mennonite communities
- “How can you help our special children?”

2012 Conference in Norwalk with Dr. Morton



Father of study of inherited disorders in the Plain population

Holmes Morton, MD

Founding Pediatrician, Clinic for Special Children,
PA

Medical Director, Central PA Clinic

UW-Madison Department of Pediatrics Grand
Rounds:

<https://www.pediatrics.wisc.edu/caring-for-the-amish-children-of-wisconsin/>

Development of expertise in genetic disorders

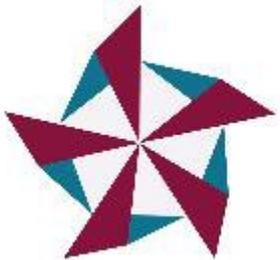
2015: Founded the Center for Special Children

2017: Established the Plain Community Health Consortium

UW Hospital and Clinics, American Family Children's Hospital

- Pediatric cardiology
- Pediatric electrophysiology
- Adult cardiology
- Biochemical genetics (medical and dietary care)
- Pediatric neurology
- Pediatric ophthalmology
- Audiology

Windows of Hope (Exeter, England): Research



Founder population



- Small number of individuals form a new community for reasons of ethnicity, religion, or geography
- Marriage occurs within their community
- Decrease in genetic variation occurs
- Some conditions absent; others may magnify in frequency

Founder populations



- >1000 founder populations (700 in India alone)
- Amish & Mennonites are distinct founder populations
- Lessons learned are applicable to populations across the world
 - Specific diseases
 - Approach to diagnosis

Deep study of disorders in a founder population



Leads to

- Pattern recognition (& institutional knowledge)
- Low cost & efficient diagnosis
- Targeted Variant development (TVARs) - \$50
- Lists of known diagnoses in a population become possible

Approach to Genetic Testing

Does this seem to be due to a genetic disorder?
Is the family interested in genetic testing?



Yes



Does the child have a recognizable syndrome?



Focused genetic test
(one gene)

Does the child have a condition with genetic causes that are well-understood



Panel of many genes related to the child's condition

Are there many possible explanations for the condition?
Has focused testing been negative?



Comprehensive genetic testing

Disorders

Metabolic disorders

- Propionic Acidemia
- Maple Syrup Urine Disease
- PKU
- Cobalamin C deficiency

Neurodevelopment disorders (severe)

- Galloway Mowat syndrome
- SNIP1
- Aicardi-Goutieres syndrome
- CNPNAP2 (caspr2)
- GM3 synthase deficiency
- BRAT1
- Pontocerebellar Hypoplasia

Neurodevelopmental syndromes (less severe)

- Troyer syndrome
- Ataxia-telangiectasia-like disorder type 2
- Amish brittle hair syndrome
- 16p11.2 duplication/deletion

Cardiovascular

- Sitosterolemia
- Hypertrophic cardiomyopathy
- Long QT2

Ocular disorders

- Oculocutaneous albinism
- Jalili syndrome
- Retinitis pigmentosa

Congenital hearing loss

- Connexin 26 (GJB2)
- SLITRK6

Respiratory/Immunologic

- Cystic Fibrosis
- Primary ciliary dyskinesia
- Cartilage hair hypoplasia
- RAG1 SCID
- DiGeorge syndrome

Miscellaneous

- Mucopolipidosis (I cell disease)
- Corticosterone Methyltransferase 1 deficiency
- DGAT1 (protein losing enteropathy)

Sporadic (not founder) mutations

- Coffin Lowrey syndrome
- Williams syndrome
- Rett syndrome
- Neurofibromatosis
- Mandibulofacial dysostosis with microcephaly
- Sturge Weber syndrome
- CHD4
- GATA3
- Smith-Magenis
- ADNP/SYNGAP1

Novel Disorders

- CHD & ocular disease
- Developmental disability w/ SNHL

Research consequences



Common Disorders:

- Large numbers; stable environment and genetics

Rare Disorders:

- Much to learn by studying single patients

Novel Disorders:

- Identified by gene sequencing; characterized clinically

Hypertrophic cardiomyopathy in Amish

Hypertrophic cardiomyopathy in the Amish



- Hundreds of mutations in a dozen genes lead to HCM phenotype
- In Amish, a single mutation in the MYBPC3 gene (c.3330+T>G) causes all HCM!
- Frequency may be as high as 1 in 20 in some populations
- Many patients (>200) with same mutation (no other similar series of patients)



Classic HCM phenotype seen, including;

- Asymmetric septal hypertrophy with LV outflow tract obstruction
- Sudden death
- Diastolic dysfunction with heart failure

Clinical presentation based on genotyping

- 90+% of patients in 20s and 30s asymptomatic and normal echo
- Pregnancy generally is uneventful (~50 deliveries without complication, including one C-section)
- With each passing decade, disease burden accumulates
- ASH & outflow tract obstruction and sudden death occur (but in minority)
- Progressive LV stiffening and diastolic dysfunction occurs
- Most patients developing cardiovascular symptoms are misdiagnosed on echo
- With onset of atrial fib, functional status declines rapidly

HCM – in summary



Sudden death and septal hypertrophy and outflow tract obstruction occur

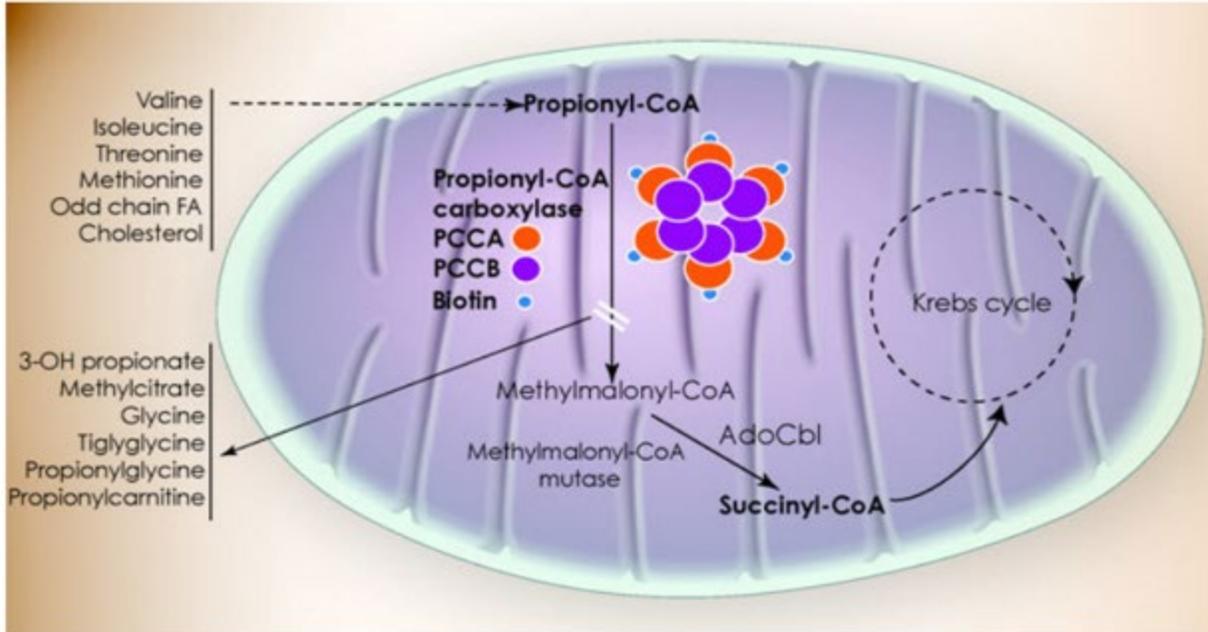
Largest burden of disease occurs in the middle years and beyond

- diastolic failure
- atrial fib
- frequent strokes
- poor functional status

Most patients are misdiagnosed based on echo alone.

Birth with propionic acidemia

Propionic acidemia



Metabolic disorder common in Amish

Krebs cycle mutation

Catabolic stress (illness; surgery; L&D) can lead to complications

- Neurologic (metabolic stroke)
- Encephalopathy
- Cardiomyopathy

Pregnancy in propionic acidemia



- No published literature
- Expertise required in neurology, cardiology, metabolic support team, OB
- Many tertiary centers will not deliver
- “Go to quaternary center!”
- Many affected patients delivering at home

Birthing with propionic acidemia



Can a safe(r) plan be developed?

- Can we deliver at our birthing center?
- Protocol developed with expertise of Waisman Center colleagues
- Consultation with multiple groups with varying expertise (none with birthing)

Birth with propionic acidemia

Protocol for delivery:

- IV D10NS to prevent dehydration
- Plus push fluids and calories
- Active labor management; minimize prolonged labor
- Monitor for urine ketones (signs of catabolism: goal NEG to trace)
- IV carnitine (increase PO carnitine at discharge)



- G1 patient with Propionic acidemia seen at 27 weeks, 33 weeks and 37 weeks
- No ultrasound for dating
- Echo at 1st visit:
 - EF 65%
 - EKG – normal QT
- Fundal height: 23cm at 27weeks (petite);
36cm at 37weeks



- SROM & onset of labor at 37 ½ weeks gestation
- Arrival 4 hours after onset of labor
- IV – D10NS at 1.5X maintenance; IV carnitine
- Urine – small ketones; became negative w/ IV fluids
- Lytes & ammonia level q4-6 hours
- At 14 hours, Pitocin augmentation started; IV ampicillin at 18' ROM
- Delivery at 20 hours S/P SROM; 3930gm
- No maternal or neonatal complications





Contents lists available at [ScienceDirect](#)

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr



Case Report

Successful pregnancy and delivery in a woman with propionic acidemia from the Amish community☆



Jessica Scott Schwoerer^{a,*}, Sandra van Calcar^b, Gregory M. Rice^a, James Deline^c

Sitosterolemia

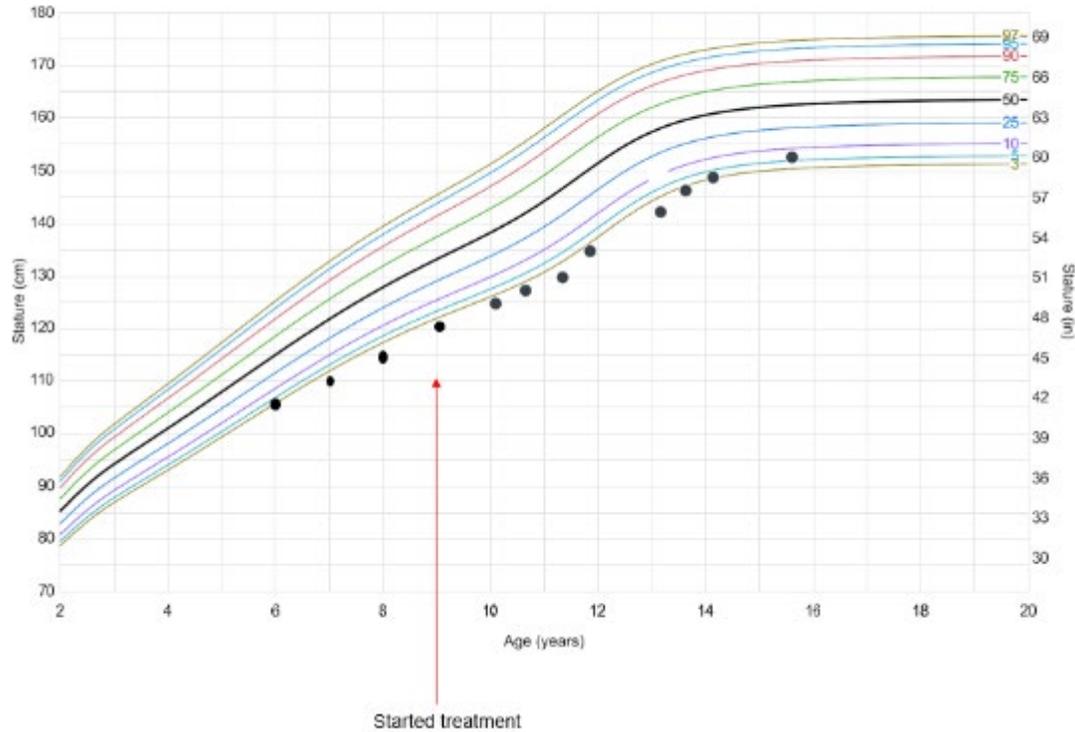
Case Description



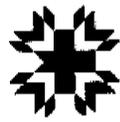
8-year-old Amish child with failure to thrive and GI bleeding

- Irritability, feeding problems from infancy
- Poor growth
- Painful legs (being pulled to school in a cart)
- Weakness
- Contact by “surrogates,” due to parental fear

Growth Chart: United States
Stature-for-age Percentiles (Girls, 2 to 20 years)



- Exam confirmed poor growth
- Otherwise normal exam
- Labs: mild normochromic anemia; normal BUN/cr; lytes; LFTs; thyroid; celiac screen; cholesterol 500
- Yellow bumps on knees; biopsy showed xanthoma



Clinic for Special Children

535 Runkel Hill Road, PO Box 128, Strasburg, PA 17579 T 717.687.9407 F 717.687.9237

DETECTION OF SPECIFIC PATHOGENIC SEQUENCE VARIANTS IN THE APOB GENE IN FAMILIAL HYPERCHOLESTEROLEMIA

CSC number	Login_date	Test date
37355	9/3/2015	9/4/2015
Pathogenic sequence variant	Protein variant	Result
APOB c.10580G>A	p.Arg3527Gln	Normal homozygote

Nomenclature: Numbering for sequence and protein variants begins with the initiation codon. Genotype nomenclature for recessive disorders is interpreted as follows: **Normal homozygote (non-carrier), heterozygote (carrier), and mutation homozygote (affected)**. For dominant disorders, heterozygotes are affected. This disease, familial hypercholesterolemia, is dominant.

Note(s): At this time, our knowledge indicates that the c.10580G>A mutation is a pathogenic sequence variant for familial hypercholesterolemia found in the Old Order Amish population. This test is specific for the c.10580G>A mutation in the APOB gene on human chromosome 2p24. This test does not detect other mutations that cause familial hypercholesterolemia.

Method: DNA is isolated by standard methods from EDTA anti-coagulated peripheral blood. A segment of DNA encoding the c.10580G>A mutation is amplified by polymerase chain reaction (PCR) using specific oligonucleotide primers. The PCR product is then sequenced using a fluorescence-based cycle sequencing protocol. The extension products are subsequently size-fractionated on an ABI 3130 Genetic Analyzer.

References: Shen et al., 2010

Erik G. Puffenberger, PhD
Laboratory Director

Kevin A. Strauss, MD
Medical Director



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535 Bunker Hill Road, PO Box 128, Strasburg, PA 17579 T 717.687.9407 F 717.687.9237

DETECTION OF SPECIFIC PATHOGENIC SEQUENCE VARIANTS IN THE *ABCG8* GENE IN SITOSTEROLEMIA

CSC number	Login date	Test date
37355	9/3/2015	9/22/2015
Pathogenic sequence variant	Protein variant	Result
<i>ABCG8</i> c.1720G>A	p.Gly574Arg	Mutation homozygote

Nomenclature: Numbering for sequence and protein variants begins with the initiation codon. Genotype nomenclature for recessive disorders is interpreted as follows: **Normal homozygote (non-carrier), heterozygote (carrier), and mutation homozygote (affected).** For dominant disorders, heterozygotes are affected. This disease, sitosterolemia, is recessive.

Note(s): At this time, our knowledge indicates that the c.1720G>A mutation is a pathogenic sequence variant for sitosterolemia found in the Old Order Amish population. This test is specific for the c.1720G>A mutation in the *ABCG8* gene on human chromosome 2p21. This test does not detect other mutations that cause sitosterolemia.

Method: DNA is isolated by standard methods from EDTA anti-coagulated peripheral blood. A segment of DNA encoding the c.1720G>A mutation is amplified by polymerase chain reaction (PCR) using specific oligonucleotide primers. The PCR product is then sequenced using a fluorescence-based cycle sequencing protocol. The extension products are subsequently size-fractionated on an ABI 3130 Genetic Analyzer.

References: Berge et al., 2000


Erik G. Puffenberger, PhD
Laboratory Director


Kevin A. Strauss, MD
Medical Director

Printed on 9/22/2015 for Outside referral.

Fasting Sterol lab report

Plasma Sterols

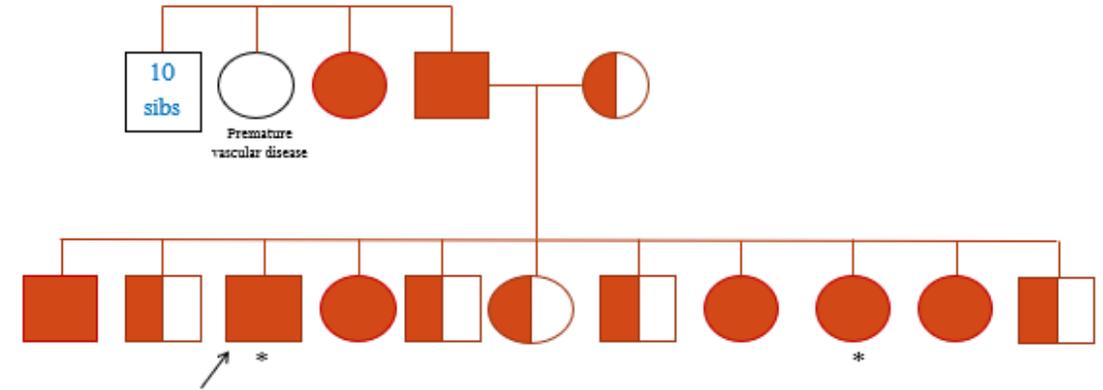
- Desmosterol: 3.3 mg/L
Reference Value: 0.0-5.0
- Lathosterol: 8.3 mg/L
Reference Value: 0.0-7.0
- Campesterol: 147.2 mg/L
Reference Value: 0.0-7.0
- **Sitosterol: 409.2 mg/L**
Reference Value: 0.0-5.0

18 month earlier...

23 y/o man with xanthomata seen in office with acute monoarticular arthritis of ankle

Pt returned with these findings:

- Xanthomata
- Painful joints, especially ankles
- Exercise limitation
- Systolic murmur with aortic valve disease
- Bruits over carotids and femoral arteries
- Targeted testing positive for sitosterolemia



* Patient with xanthomata

- 6 out of 12 children homozygotes
- Others all carriers
- Father homozygote; mother carrier
- Sister, affected, currently pregnant (22 weeks)
- Three consecutive teenage sisters affected
- 14 y/o sister w/ aortic outflow murmur & bruits over all major arteries

Sitosterolemia (phytosterolemia)



- Disorder of plant sterol metabolism leading to dramatic elevation in levels, esp. sitosterol and campesterol
- Accelerated atherogenesis
- Hematologic effects
- ~ 100 reported cases
- Seen in Amish, Hutterites, Chinese, Korean, Middle East

Sitosterolemia (phytosterolemia)



- Mutation in gene ABCG5 or ABCG 8
- Many mutations result in same phenotype
- Amish founder mutation (ABCG8 c.1720G>A)
- Sterol levels 50 to 200X normal

Clinical features



- Accelerated atherogenesis (& aortic valve disease)
- Xanthomata
- Hematologic (hemolytic anemia; large platelets); bleeding risk?
- Orthopedic (lower extremity arthritis; Achilles' tendonitis)
- GI distress & poor growth (in subset)

Treatment

- Statins ineffective
- Ezetimibe quite effective
- Diet low in plant sterol

Food Group	High-Sterol Foods to Limit or Avoid	Recommended Low-Sterol Foods
Fats/Oils	canola oil, corn oil, sesame oil, sunflower oil	lard, butter, coconut oil
Nuts/Seeds	peanuts, almonds, walnuts, sunflower seeds, sesame seeds	hazelnuts, macadamia nuts, pumpkin seeds
Fruits	apples, avocados, blueberries, grapes, oranges, raspberries	bananas, plums, pears, strawberries
Vegetables	broccoli, cauliflower, cucumbers, peas, dried beans, lentils	onions, potatoes, tomatoes, spinach, carrots, beets, sweet corn
Grains	whole wheat bread, brown rice, rye bread	white bread, white rice, barley, rolled oats, corn flakes
Dairy	yogurt with plant sterols, margarine	butter, milk, cheese, yogurt without plant sterols
Meat	shellfish	all meats

Xanthomata, before and after treatment



OB Management?



- No literature (sitosterolemia or homozygous FH)
- Fetal risks?
 - Doppler flow studies
 - Placental pathology
- Maternal risks?
 - Bleeding risk? Platelet function abnormalities?
 - Adrenal insufficiency?
 - Risk of acute MI or stroke intrapartum?

Labor & Delivery course



- 16-hour 1st stage, 3-hour 2nd stage
- Blood loss measured – normal
- APGARs normal
- Placenta examined & placed in formalin for shipping to Boston

Research Questions

Diagnosis: pre- and postprandial sterol panels

Enriching phenotype:

- GI issues
- Xanthomata frequency

OB care:

- No literature
- Fetal doppler study
- Platelet function studies
- Placental pathology

Measuring treatment impact:

- Sterol levels
- Symptoms
- Xanthomata
- CIMT

New treatments:

- Bile acid sequestrants?
- Stanols (Benecol)?
- Administering “smart” probiotic replacing missing brush border enzyme?

Novel Disorders



TGFBR3 mutation: ophthalmologic disease;
congenital heart

FRY mutation: sensorineural hearing loss;
intellectual disabilities

DIXDC1: heterotaxy, ciliopathy; developmental
delay

SLC25A4: obesity (Prader-Willi like) and
development delay

Questions?

“Special children are not just an interesting medical problem, subjects of grants or research. Nor should they be called burdens to their families and communities.

They are children who need our help and, if we allow them to, they will teach us compassion.

They are children who need our help, if we allow them to, they will teach us to love.

If we come to know these children as we should, they will make us better scientists, better physicians, and more thoughtful people.”

