



### Newborn and carrier screening in southwestern Ontario FORGE Canada – a history of collaboration

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### Anabaptist groups in SW Ontario

Old Order Mennonite

Old Order Amish

Old Colony Mennonite



## In the beginning...



- High fever precipitates visual hallucinations and psychosis, eventual hearing loss and pigmentary retinopathy
- Sudden death
- Now ID'd as HARS

### Collaboration with The Clinic for Special Children in Pennsylvania -Dr. Holmes Morton





# Migration of Old Order Amish (in <u>Aylmer</u>, Ontario) and Old Order Mennonites



First settled in Pennsylvania, then migrated to Ontario after 1776

Many ties to American families

Many disorders shared between Ontario and Pennsylvania

Maple syrup urine disease Spinal muscular atrophy Amish microcephaly Pretzel syndrome Specific mutation identified for 9 disorders in Old Order Amish in population of about 1200

Specific mutation identified for 10 disorders in Old Order Mennonite population of about 2500

## Migration of Amish to Perth County, Ontario



Immigrated directly to Canada from Alsace-Lorraine (France) and Bavaria beginning in 1825

Genetically isolated from American Amish

## Many disorders unique to Old Order Amish in Ontario, not seen in Lancaster Amish

- Cerebral atrophy syndrome
- Fraser syndrome
- ECO syndrome
- Sodium diarrhea

# Collaboration with European colleagues (A. Janecke)



### Migrations of the Old Colony Mennonites to Ontario



# **Old Colony Mennonites**

- Largest group in Ontario, with many assimilated into general population
- Often not aware of their genealogy
- Many migrate between Mexico (winter) and Canada (summer)
- Difficult to provide consistent medical care and investigate for genetic disorders

# Old Colony (Low German speaking) Mennonites

- 3 different types of SCID
  - ZAP70 kinase
  - CD3 delta
  - ADA deficiency

## SCID screening in Ontario to begin in August 2013 for entire population (part of Ontario Newborn Screen)



- Will be screening with TRECs
- Benefits Mennonite and non-Mennonite babies

 See list of Amish and Mennonite disorders in Ontario

# The Amish newborn screening project:



- Population about 1200
- About 200 families
- 30-40 newborns each year

### 2004: Newborn DNA testing for treatable disorders in the Amish community of Perth County

initiated following discussions with community leaders, public health providers, and midwives

research funding was obtained for a pilot project

disorders chosen were all amenable to treatment

### **Disorders screened:**

- Juvenile glaucoma (2 mutations)
- Cystinosis.
- Cystic fibrosis (2 mutations)
- Galactosemia

### The cord blood sampling kit

instructions and requisition



blood dot card



courier package

gloves

mailing container

5 cc tube

# Targeted newborn screening in the Old Order Amish

 370 babies (90%) have been screened using a combination of biochemical and DNA based analysis for targeted mutations

# Outcomes of targeted newborn screening

Detected one child affected with each of the disorders out of 370 screened

High carrier rate in newborns tested

- cystinosis 1:5
- cystic fibrosis 1:7
- galactosemia 1:7
- glaucoma 1:11

Has been incorporated into routine care

### Screening led to reporting of other disorders: Out of 92 consecutive pregnancies:

- 5 lethal anomalies: 3 ECO, 2 Fraser syndrome with renal agenesis
- 1 cystic fibrosis
- 1 oligodactyly
- 1 stillbirth at term
- 3 cleft palates

 2 with cerebral atrophy and neurodevelopmental regression

# Limitations of targeted newborn screening

- Turnaround time for DNA results
- Amish Newborn screen is only applicable for Amish infants
- Other treatable genetic disorders in the population are not routinely screened
- Inefficient to test one gene at a time
- Increasing number of disorders identified

### **Carrier screening of newborns**

- Occurs automatically with DNA testing
- Bishops have decided that carrier status is not to be revealed

## What about adult carrier testing?

- If we test married couples and find that they are not carriers for the same disorder, none of their offspring are at risk, and therefore their babies do not need to be tested for the disorder
- If a couple is at risk, we can do targeted testing ASAP after birth to identify affected babies while still asymptomatic

# Family members began requesting adult carrier testing

- Clinics were held for testing of large groups for single disorders
  - Galactosemia (OOA)
  - Glaucoma (OOA)
  - HLH (OOM)
  - MSUD (OOM)
- Inefficient to test individual genes as often carriers for more than one disorder

## **Current strategy**

- Research grant to develop TaqMan assay to screen for 14 Amish and Mennonite disorders at the same time
- Offer testing to married couples
- If not at risk to have any of the disorders, no targeted testing of newborn will be done
- At-risk babies will be rapidly tested for specific disorder

### Maple syrup urine disease: Tale of two babies

PLASMA LEUCINE CONCENTRATIONS SINCE BIRTH 3500 \$50,000 3000 2500 -SYMPTOMATIC MN DIAGNOSIS 2000 -EUCINE PRESYMPTOMATIC DIAGNOSIS 1500 1000 <\$1000 500 0 Hospitalizatio n

### **Ethical concerns**

- Do married couples want to know their carrier status?
- Do couples want to have a child diagnosed before symptoms occur if there is no treatment? (eg SMA)

# A potential clinical trial for treatment of SMA



Isis Pharmaceuticals is developing a drug to treat Spinal Muscular Atrophy (SMA). SMA is a genetic neuromuscular disease characterized by muscle atrophy and weakness. SMA is a leading genetic cause of infant mortality. According to the National Institutes of Health, one child out of approximately every 6,000 to 10,000 births is born with SMA. There are approximately 30,000 – 35,000 patients with SMA in the United States, Europe and Japan. Currently, there are no approved drug treatments available for patients with SMA.

#### Understanding Survival Motor Neuron 1 & Its Role in SMA

SMA is caused by a loss of or defect in the survival motor neuron 1 (SMN1) dene. The SMN1 dene produces most



### Clinical exome sequencing: Transforming the care of patients with rare genetic diseases

### Kym Boycott, PhD, MD, FRCPC, FCCMG

Children's Hospital of Eastern Ontario Research Institute University of Ottawa, Canada

### More disorders to be discovered!



gene known

### gene unknown

### FORGE Canada Consortium





## What disorders do we study?

>400 Diseases Proposed

![](_page_34_Figure_2.jpeg)

>200 Diseases Selected for Study

"AND THE VOTE TO HAVE A UNANIMOUS CONSENSUS PASSED FIVE TO TWO."

- Congenital or develops in childhood or adolescence
- Disorder is likely monogenic and gene unknown
- At least one Canadian patient with condition available for study
- Appropriate investigations have been performed to exclude known causes

# Data generation and analysis

![](_page_35_Picture_1.jpeg)

3 centres for exome sequencing

Project Teams -validation studies-

National Data Coordination Centre

![](_page_36_Picture_0.jpeg)

### 101 Disorders into pipeline ...

![](_page_36_Figure_2.jpeg)

3 Approaches

# Approach 1- Mapping

![](_page_37_Figure_1.jpeg)

![](_page_37_Figure_2.jpeg)

![](_page_37_Figure_3.jpeg)

## ECO syndrome (endocrine-cerebroosteodysplasia)

![](_page_38_Figure_1.jpeg)

## Approach 2 – Multiple Alleles

![](_page_39_Figure_1.jpeg)

## Approach 3 - Sibpairs

![](_page_40_Figure_1.jpeg)

Nonconsanguineous families – AR disorder

![](_page_40_Picture_3.jpeg)

http://www.ottawacitizen.com/technology December 4, 2011

Genes with missense, nonsense, indel or splice variants	6453
Genes with rare mutations *	372
Genes with mutations shared by sibs	109
Genes with homozygous/ multiple heterozygous variants	2

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### Success rate with FORGE

- Out of 101 samples:
  - About 1/3 had unique disorder in new gene
  - About 1/3 had mutation in known gene
  - About 1/3 unsolved

# FORGEing On! Enhanced CARE for RARE Genetic Diseases in Canada

### Kym Boycott, PhD, MD Alex MacKenzie, PhD, MD

Children's Hospital of Eastern Ontario Research Institute University of Ottawa, Canada

### **CARE for RARE** Overview

![](_page_43_Figure_1.jpeg)

![](_page_44_Picture_0.jpeg)

- Single case
- Presumed de novo

![](_page_44_Figure_3.jpeg)

### **CARE for RARE** Team

![](_page_45_Figure_1.jpeg)

## Can we design a similar pipeline together to share phenotypes, identify genes, and look at treatments?

![](_page_47_Picture_0.jpeg)

### Amish, Mennonite, and Hutterite Genetic Disorder Database

http://www.biochemgenetics.ca/plainpeople/

### **Benefits of the database**

 Ability to search on symptoms to aid in the diagnosis of a rare disorder

### Please let us know about your publications and gene discoveries to enter into the database Also, let us know about your unknowns

![](_page_49_Picture_1.jpeg)

Canadians know how to play together in the sandbox (K. Boycott)

![](_page_50_Picture_0.jpeg)

### Thank you

![](_page_50_Picture_2.jpeg)

![](_page_50_Picture_3.jpeg)

- CSC
- Jane Leach
  PHN extraordinaire
- Piya Lahiry
- Sali Farhan
- The families, midwives, physicians, laboratory staff