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

Tony Rupar, Victoria Siu, Robert Hegele, Kym Boycott
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 Aylmer, 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)

Identification of gene for sodium diarrhea
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
- Courier package
- Gloves
- Mailing container
- 5 cc tube
- Needles, syringe
- Blood dot card
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

\[ \frac{13}{92} = 14\% \] with major anomalies
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

- **Symptomatic Diagnosis**
- **Presymptomatic Diagnosis**

- Hospitalization
- $50,000
- <$1000
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

Spinal Muscular Atrophy & ISIS-SMN<sub>Rx</sub>

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) gene. The SMN1 gene 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

Disorders to Study

Core Element Consent

Gene Discovery

Knowledge Translation

National Data Coordination

Guidelines for Return of Incidental Findings

2 year project
April 2011 to March 2013
Finding Of Rare Disease GEnes

FORGE Canada Consortium
Dr. Gudrun Aubertin
Dr. Jan Friedman
Dr. Francois Bernier
Dr. Ordan Lehman
Dr. Bridget Fernandez
Dr. Sarah Dyack
Dr. Edmond Lemire
Dr. Albert Chudley
Dr. Victoria Siu
Dr. Malgorzata Novaczyk
Dr. Marjan Nezarati
Dr. Linda Kim

Toronto
Montreal

21 Sites
80 Physicians
50 Scientists
What disorders do we study?

>400 Diseases Proposed

>200 Diseases Selected for Study

- 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

3 centres for exome sequencing

Project Teams -validation studies-

National Data Coordination Centre
101 Disorders into pipeline ...

3 Approaches

- Multiple alleles
- Mapping data
- Compound heterozygous
Approach 1 - Mapping

Consanguineous families

AD families with multiple affected members
ECO syndrome
(endocrine-cerebro-osteodysplasia)
Approach 2 – Multiple Alleles

Unrelated patients with same disorder

Unrelated families with same disorder AR, AD, X-L

Coding Variants

Rare Coding Variants

Shared Rare Coding Variants

2 Patients

Shared

3

Shared

4

EFTUD2
Approach 3 - Sibpairs

Nonconsanguineous families – AR disorder

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<tr>
<th>Description</th>
<th>Count</th>
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<td>Genes with missense, nonsense, indel or splice variants</td>
<td>6453</td>
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<tr>
<td>Genes with rare mutations *</td>
<td>372</td>
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<tr>
<td>Genes with mutations shared by sibs</td>
<td>109</td>
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<tr>
<td>Genes with homozygous/ multiple heterozygous variants</td>
<td>2</td>
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</table>

http://www.ottawacitizen.com/technology

December 4, 2011

c.101C>T; p.A34V

c.1547T>C; p.I516T
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

Canadian Patients with Rare Diseases

Expand Human Mutation Atlas

Clinical Exome Workflow

ID Therapeutic Opportunities

Molecular Diagnosis

Optimized Platform

Enhanced Care
Approach 4 – exome sequencing of trios

- Single case
- Presumed de novo
CARE for RARE Team

- Toronto
- Montreal
- CARE for RARE Team
- GE 3 LS
- Pfizer Inc.
- Rare Disease Research Unit
- Dr. Kevin Lee
- 21 Sites
- 80 Physicians
- 50 Scientists
Can we design a similar pipeline together to share phenotypes, identify genes, and look at treatments?
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

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

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