Clinical Genetics and the Hutterite Brethren: What have we learned in the new millenium?

Or:

A Micheil Innes MD FRCPC FCCMG
Adapted from: Medical Genetics Grand Rounds
January 2013
History and Population

Hutterite Population

Today
>40 000 in AB, MB, ND, SD

1500s
Tyrolean Alps

1565-1592
Moravia

1593-1770
Transylvania

1770 - 1870
Ukraine

1874-1879
1256 migrated to American Prairies

World War I
Migration to Canada

1520
1540
1550
1570
1580
1590
1610
1620
1680
1750
1840
1860
1890
1900
1950
1975
1990

0
5000
10000
15000
20000
25000
30000

1565-1592
1770 - 1870
1874-1879
Why Identify Genes in this Population?

• Direct Benefits to Patients/Families
  – Non-invasive diagnostic test
  – Carrier test (*marriage restrictions)
  – ?Prenatal testing
  – Enhanced understanding of disease may facilitate management or treatment

• Benefit to Larger population
  – Most of these disorders are not confined to this population
  – May allow for diagnosis of atypical cases
  – Expand basic science and clinical knowledge
Initial Presentations May be Non-Specific Highlighting Importance of Careful Syndrome Delineation and Early Genetic Diagnosis

- **Hearing Loss**
  - Autosomal recessive non-syndromic hearing loss (> 2 loci)
  - Usher syndrome (> 2 loci)
  - HDR syndrome

- **Cerebellar Ataxia**
  - Joubert syndrome
  - DES syndrome
  - DCMA syndrome
  - CASS syndrome

- **Muscular Dystrophy/ High CK**
  - LGMD2H
  - LGDM2I
  - AR EDMD
  - Myopathy with CPEO
  - Microcephaly with Chorea
Genetic services and the Hutterites
Religion/Culture

• Has posed little barrier overall

• Very accepting of medical care and technology

• Although they believe that God plays a day to day role in guiding their lives, most couples accept genetic explanations for their children’s disorders

• Some leuts and individual colonies are more conservative than others

• Colony leader is clearly the Minister

• Who speaks for the overall community when it comes to community wide issues? – e.g. newborn screening, research
Selma Maendel, Winnipeg, September 2006

“...should we become informed in the name of being proactive?...In the near future should Hutterites come for across the board genetic testing before marriage?...Hutterites temporarily waive the right to individual choice, the needs of the community must sometimes come before our own...showing respect for our approach will encourage our elders to respect yours...”

“Together we (researchers and Hutterite adults) make a ‘considerable man’ when it comes to the care of Hutterian Children”
Clinical Medicine and the Hutterites- 1953-1975

• 1967- “General Tom Thumb and other midgets” McKusick VA and Rimoin DL. Scientific American 217:103-10.

“...there is little evidence to suggest that Hutterites have more hereditary diseases....and perhaps they have fewer hereditary diseases than other isolates, for example, the Old Order Amish. There are least six dwarfs and perhaps as many as twenty-four albinos among the Hutterites” Hostetler, 1974
Workshop on Genetic Disorders in the Hutterites-
Edmonton, Canada, October 12-13, 1983
+ 7 other companion papers!

- Methylmalonic aciduria
- Juvenile Cataract
- Mandibulofacial dysostosis
- MPS IVa
- Hypophosphatasia
- Cerebro-Osteo-Nephrodysplasia
- Congenital Contractures (Restrictive dermopathy)
- Cystic Fibrosis
- Panhypopituitary syndrome
- Bowen-Conradi syndrome
- Meckel Syndrome
- Dysequilibrium syndrome
- Muscular Dystrophy
- Leigh disease
- Sensorineural deafness
- Iodide transporter defect
- Maple syrup urine disease
## Hutterite Population

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<th>Name of disorder or trait</th>
<th>Abbreviation</th>
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**Research Review**

Clinical Genetics and the Hutterite Population: A Review of Mendelian Disorders

Kyna M. Boycott,1,2* Jillian S. Parboosingh,3 Bernie N. Chodirker,3 R. Brian Lowry,2 D. Ross McLeish,3 Jack M. Morris,3 Cheryl R. Greenberg,5 Albert E. Chudley,5 Françoise P. Berrié,4 Julian Whitley,7 Linda Dehl Molenaar,7 and A. Michael Haines6

30 recessive disorders
Gene known for 50%

Unreported, novel disorders – 10+
~50 different autosomal recessive conditions/mutations present in the Hutterite population

**Gene/Mutation Identified (30)**
- Albinism
- ARVC
- Autoimmune Polyendocrinopathy
- **Bardet-Biedl**
- Bowen-Conradi
- Congenital Hyperinsulinism
- CPT1 deficiency
- CF (x2)
- **DCMA**
- Deafness (x2)
- Dysequilibrium syndrome
- Emery Dreifuss Muscular Dystrophy
- Iodide transporter defect
- **Leigh disease**
- LGMD2H, LGMD2I
- Hypophosphatasia
- MMA
- MSUD
- **Meckel-Gruber/Joubert (x2+)**
- Nephronophthisis (x2+)
- Panhypopituitarism
- **Restrictive Dermopathy**
- Sitosterolemia
- Succinylcholinesterase deficiency (x2)
- Usher (x2)

**Gene/Mutation Not yet published (9)**
- Alveolar capillary dysplasia with limb deficiency
- CASS
- Chromosomal breakage syndrome
- Cranoectodermal dysplasia
- Dihydropyrimidine dehydrogenase
- **FARR**
  (2 Joubert genes, 1 probable NPHP gene)
- Microcephaly/Myopathy

**Gene/Mutation Not yet known (14)**
- Asphyxiating Thoracic Dystrophy
- Cataracts
- Cerebro-osteo-nephro dysplasia
- CPEO with myopathy
- Cutis Aplasia
- Morquio
- Neonatal Epileptic Encephalopathy
- Nephrotic Syndrome/Immunodeficiency
- Periodic Fever Syndrome
- Rubinstein Taybi syndrome
- Storage Disorder
- Syndromic Congenital Heart Disease
- Syndromic Diaphgramtic Hernia
- Van Buchem Disease

Plus MANY Undiagnosed “Sporadic” patients!
Workshop on Genetic Disorders in the Hutterites-Edmonton, Canada, October 12-13, 1983

- Methylmalonic aciduria
- Juvenile Cataract
- Mandibulofacial dysostosis*
- MPS IVa
- Hypophosphatasia
- Cerebro-Osteo-Nephrodyplasia
- Congenital Contractures (Restrictive dermopothy)
- Cystic Fibrosis
- Panhypopituitary syndrome
- Bowen-Conradi syndrome
- Meckel Syndrome (*Joubert)
- Dysequilibrium syndrome
- Muscular Dystrophy
- Leigh disease
- Sensorineural deafness
- Iodide transporter defect
- Maple syrup urine disease

*not autosomal recessive

Update to 2013
Summary

Autosomal recessive developmental disorders

Genome-wide SNP analysis
- Identity-by-descent mapping

Sanger sequencing

 Identify and sequence candidate genes

Disease-gene identification

Diagnostic testing
Identification of syndrome in non-Hutterite children
Carrier testing
Future Directions

- Identify and sequence candidate genes
  - Next-Gen sequencing
  - Novel gene identification
    - Developmental pathways

JS gene
www.stjudebgem.org

THOC6

ZIP8
PNAS 2005; 102:3401
Molecular Diagnostic Testing for Genetic Disorders in the Hutterite Population

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<th>Gene</th>
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Bowen Conradi Syndrome, Birt-Hogg-Dube syndrome, ARVC, BBS, MODY- also clinically available JSRD (TMEM237), Restrictive Dermopathy, Albinism, LGMD2H, LGMD2I- under development

*Calgary – Molecular Diagnostic Laboratory, Alberta Children’s Hospital; Edmonton – Molecular Diagnostic Laboratory, University of Alberta; Winnipeg – Molecular Diagnostic Laboratory, Diagnostic Services of Manitoba
Welcome to the Amish, Mennonite, and Hutterite Genetic Disorders Database

Funding for the creation of this website was provided in part by The Change Foundation.

Site designed by Geoffrey Stru, August 2005.
Site maintained by Biochemical Genetics Laboratory, London, Ontario.
This page last updated: 2008-02-04.
A Population-Based Study of Autosomal-Recessive Disease-Causing Mutations in a Founder Population

Jessica X. Chong,1,* Rebecca Ouenga,1 Rebecca L. Anderson,1 Darrel J. Waggoner,1,2 and Carole Ober1,3,*

Table 1. Thirteen AR Diseases and the Corresponding 14 Mutations in the Hutters

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Table 2. Results of Carrier Screening for 14 AR Mutations in 1,664 Hutters from South Dakota

<table>
<thead>
<tr>
<th>Disease</th>
<th>MIM Number</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Mutation (Exon Name)</th>
<th>Mutation (IVS Name)</th>
<th>Reference Cluster ID</th>
<th>Group</th>
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<tbody>
<tr>
<td>Limb-girdle muscular dystrophy 2H</td>
<td>228</td>
<td>5</td>
<td>CTFR</td>
<td>F586delI</td>
<td>NM_002012.3 (c.1551_1552delCTTT)</td>
<td>NM020068633</td>
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<tr>
<td>Occulocutaneous albinism type A</td>
<td>180</td>
<td>3</td>
<td>TYR</td>
<td>p.Cys913Pro</td>
<td>NM_002012.3 (c.270C&gt;G)</td>
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<td>Spinal muscular atrophy type III</td>
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<td>SMA</td>
<td>exon 7 del</td>
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<td>N.A.</td>
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This table is ordered by carrier frequency. The combined carrier frequency for cystic fibrosis (0.1521_1523delCTTT + c.172delG) is 0.0517 (1 in 19). We do not perform carrier screening in the existing literature.

Range TRIM32/LGMD2H 1/6.5 to dF508 1/45.5
SMA SMN del exon 7: 1/8 versus 1/35
LGMD2I FKRP L276I: 1/9.5 versus 1/300
Deafness GJB2 del35G: 1/28 versus 1/40
CF CFTR dF508 1/45.5 versus 1/30
Hutterite Carrier Chip

Development of a Diagnostic Chip for the Hutterite Population
TL Dyck¹, B Triggs-Raine², CR Greenberg²,³, C Ober⁴, JS Parboosingh⁵, AM Innes⁵, B Gerull⁶, K Boycott⁷, EL Spriggs¹,² ¹Clinical Biochemistry and Genetics, Diagnostic Services of Manitoba, Winnipeg, Manitoba, Canada, ²Departments of Biochemistry & Medical Genetics and Pediatrics & Child Health, University of Manitoba, Winnipeg, Manitoba, Canada, ³Child Health Program, Winnipeg Regional Health Authority, Winnipeg, Manitoba, Canada, ⁴Department of Human Genetics, University of Chicago, Chicago, Illinois, United States, ⁵Department of Medical Genetics, University of Calgary, Calgary, Alberta, Canada, ⁶Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada, ⁷Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada
Partial list of Genetic Conditions for which treatment is available

- DCMA syndrome
- CPT1 deficiency
- Cystic Fibrosis
- Dihydropyrididimine dehydrogenase deficiency
- Emery Dreifuss Muscular Dystrophy/Familial Partial lipodystrophy Dunigan type
- Iodide transporter defect
- Hypophosphatasia
- Methylmalonic aciduria
- Nephronophphthisis
- Panhypopituitarism
- Congenital deafness
- Usher syndrome
- Autoimmune Polyendocriniopathy syndrome
- Hereditary Breast Cancer
- Arrhythmogenic Right Ventricular Dysplasia
- Hypoparathyroidism Renal Dysplasia Deafness
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- Dr Erik Puffenberger and the Clinic for Special Children, Dr Carole Ober, Jessica Chong
- Clinical Geneticists and Metabolic Physicians, Genetic Counselors and Lab Staff Department of Medical Genetics
- Dr Cheryl Greenberg, Dr Klaus Wrogemann and Geneticists University of Manitoba
- Patients and families and Hutterite Communities of Alberta and Manitoba