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

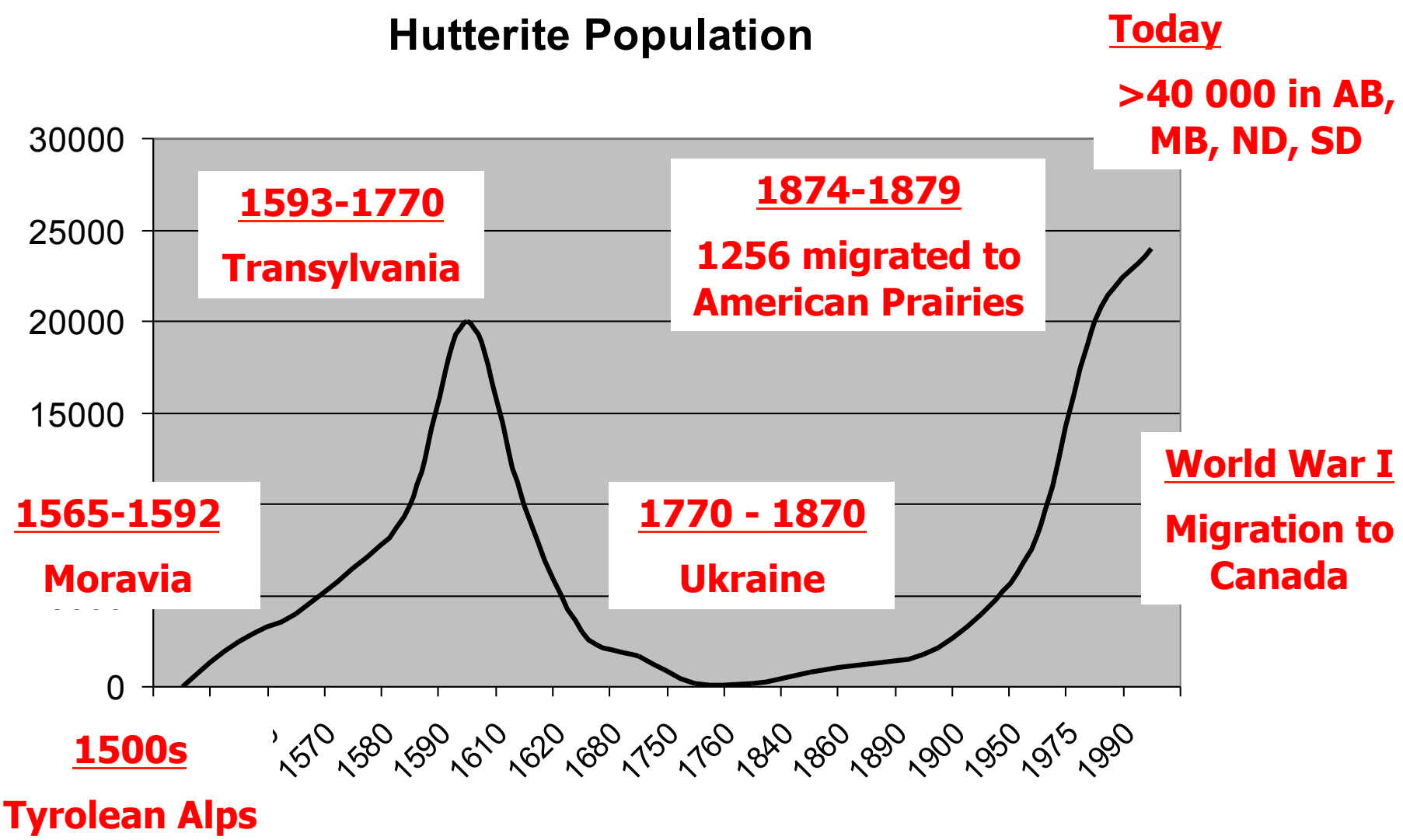
Or:

A Micheil Innes MD FRCPC FCCMG

Adapted from: Medical Genetics Grand Rounds

January 2013

History and Population



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 (> 2loci)
  - Usher syndrome (> 2loci)
  - 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

A Hutterite Perspective

- 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

- 1953- “The Mental Health of the Hutterites” Weil and Eaton, Scientific American 189: 31-7.
- 1967- “General Tom Thumb and other midgets” McKusick VA and Rimoin DL. Scientific American 217:103-10.
- 1969- “Congenital heaert disease among the Hutterite Brethren” Lee TV and Buker RS Jr, NEJM 280: 1061-2.

“…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

Bowen, Am J Med Genet 22: 449-51 1985

+ 7 other companion papers!

- **Methylmalonic aciduria**
- **Juvenile Cataract**
- **Mandibulofacial dysosostosis**
- **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

Name of disorder or trait	Abbreviation	OMIM	Gene/locus	Mutation
Autosomal recessive				
Bardet–Biedl syndrome	BBS	209900	—	—
Bowen–Conradi syndrome	BCS	211180	12p13.3	—
Carnitine Palmitoyltransferase I deficiency	CPT1	255120	*CPT1A*	G710E
Cataracts (juvenile)	JC	212500	—	—
Cerebro-osteo-nephrodysplasia	COND	236450	—	—
Combined pituitary hormone deficiency	CPHD	262600	*PROP1*	301_302delAG
Cystic fibrosis	CF	219700	*CFTR*	F508del, M1101K
Dilated cardiomyopathy with ataxia syndrome	DCMA	610198	*DNAJC19*	IVS3-1G-C
Dihydropyrimidine dehydrogenase def	DPD	274270	—	—
Dopa-responsive dystonia	DRS	605407	*TH*	T494M
Dysequilibrium syndrome	DES-H	224050	*VLDLR*	deletion
Hyperkeratosis-contracture syndrome		275210	—	—
Hypophosphatasia		241500	*ALPL*	G317D
Iodide transporter defect	ITD	274400	*SLC5A5*	G395R
Joubert syndrome/Meckel syndrome	JSRD	—	—	—
Leigh disease		256000	—	—
Limb girdle muscular dystrophy 2H/Sarco-tubular myopathy	LGMD2H	254110	*TRIM32*	D487N
Limb girdle muscular dystrophy 2I	LGMD2I	607155	*FKRP*	L276I
Mandibulofacial dysostosis		248390	—	—
Maple syrup urine disease	MSUD	248600	—	—
Methylmalonic aciduria	MMA	251000	—	—
Morquio syndrome		253000	—	—
Nephronophthisis—juvenile	JNPHP	256100	*NPHP1*	290 kb deletion
Oculocutaneous albinism (type unknown)	OCA	—	—	—
Sensorineural deafness		—	—	—
Sitosterolemia		210250	*ABCG8*	S107X
Spinal muscular atrophy type III	SMA	253400	*SMN1*	hom del
Succinylcholine sensitivity		177400	*BCHE*	D70G, A539T
Usher syndrome Type 1F	USH1F	602083	*PCDH15*	1471delT
Van Buchem syndrome		239100	—	—

American Journal of Medical Genetics Part A 146A:1088–1098 (2008)

Research Review

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

Kym M. Boycott,[1]* Jillian S. Parboosingh,[2] Bernie N. Chodirker,[3] R. Brian Lowry,[2] D. Ross McLeod,[2] Jackie Morris,[4] Cheryl R. Greenberg,[3] Albert E. Chudley,[5] Francois P. Bernier,[2] Julian Midgley,[5] Lisbeth Birk Møller,[6] and A. Micheil Innes[2]

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
Succinlycholinesterase deficiency (x2)
Usher (x2)

Gene/Mutation Not yet published (9)

Alveolar capillary dysplasia with limb deficiency
CASS
Chromosomal breakage syndrome
Cranioectodermal 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-nephrodysplasia
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

Bowen, Am J Med Genet 22: 449-51 1985

- Methylmalonic aciduria
- Juvenile Cataract
- **Mandibulofacial dysosostosis***
- MPS IVa
- Hypophosphatasia
- Cerebro-Osteo-Nephrodysplasia
- Congenital Contractures (Restrictive dermopathy)
- **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**

GENE AND MUTATION KNOWN
ALLELIC HETEROGENEITY
LOCUS HETEROGENEITY
SHARED MUTATION WITH MENNONITES

*not autosomal recessive

Update to 2013

Summary

Autosomal recessive developmental disorders

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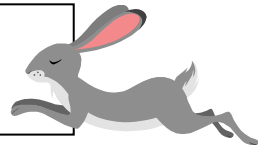
Genome-wide SNP analysis
- Identity-by-descent mapping



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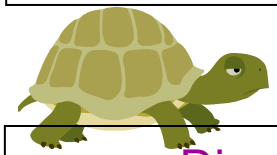
Sanger sequencing → Identify and sequence candidate genes



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Disease-gene identification

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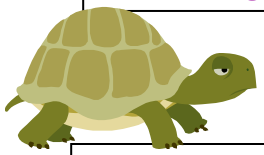
Diagnostic testing
Identification of syndrome in non-Hutterite children
Carrier testing

Future Directions

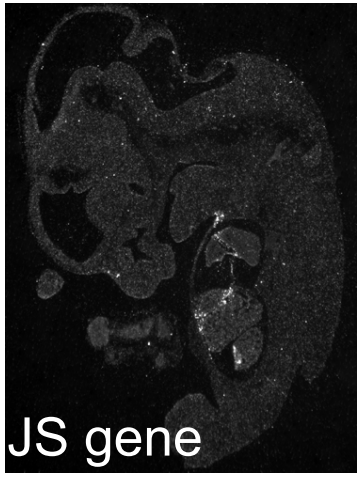
Identify and sequence candidate genes

Next-Gen sequencing

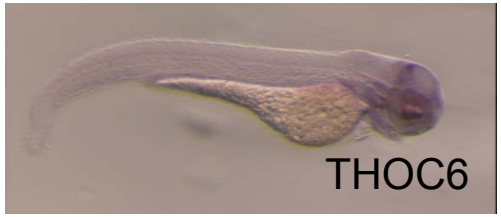
Novel gene identification

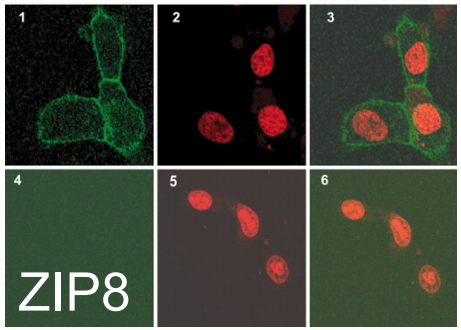


Developmental pathways



www.stjudebgem.org





PNAS 2005; 102:3401

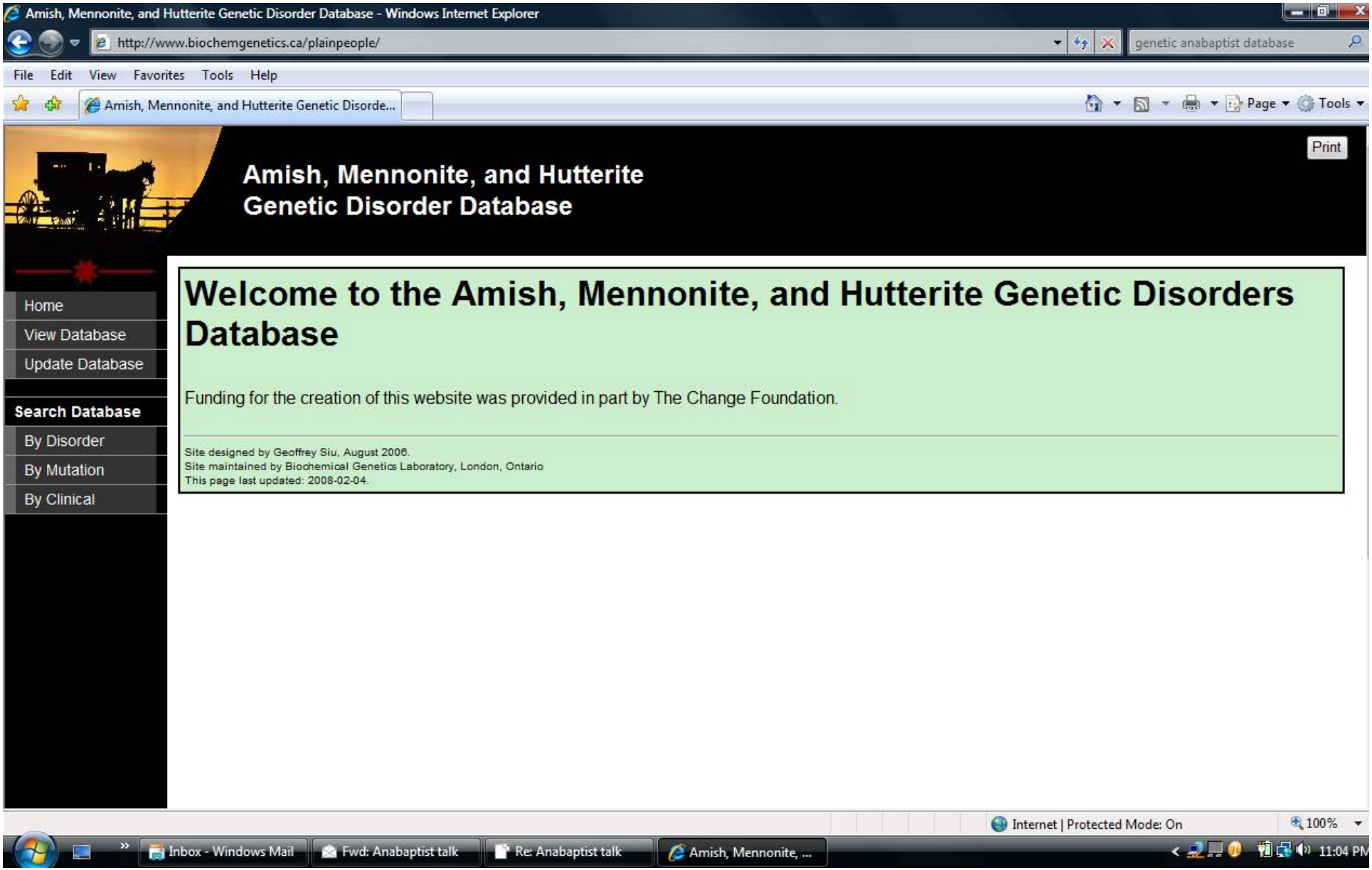
Molecular Diagnostic Testing for Genetic Disorders in the Hutterite Population

Name of Disorder or Trait	Abbreviation	OMIM	Gene	Mutation	Laboratory*
Autosomal recessive					
Cystic fibrosis	CF	219700	CFTR	F508, M1101K	Calgary, Winnipeg
Dilated cardiomyopathy with ataxia syndrome	DCMA	610198	DNAJC19	IVS3-1G>C	Calgary
Dysequilbrium syndrome	DES-H	224050	VLDLR	deletion	Calgary
Hypophosphatasia		241500	ALPL	G317D	Winnipeg
Limb girdle muscular dystrophy 2H/ Sarcotubular myopathy	LGMD2H	254110	TRIM32	D487N	Winnipeg
Limb girdle muscular dystrophy 2I	LGMD2I	607155	FKRP	L276I	Winnipeg
Nephronophthisis – juvenile	NPHP1	256100	NPHP1	250 kb deletion	Calgary
Panhypopituitarism		262600	PROP1	301-302delAG	Calgary
Spinal muscular atrophy type III	SMA	253400	SMN1	homozygous del	Calgary, Edmonton, Winnipeg
Autosomal dominant					
Breast Cancer	BRCA1	113705	BRCA1	R1443X	Calgary, Edmonton, Winnipeg
Breast Cancer	BRCA2	600185	BRCA2	7671delT	Calgary, Edmonton, Winnipeg

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

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



A Population-Based Study of Autosomal-Recessive Disease-Causing Mutations in a Founder Population

Jessica X. Chong,[1,*] Rebecca Ouwenga,[1] Rebecca L. Anderson,[1] Darrel J. Waggoner,[1,2] and Carole Ober[1,3,*]

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

Disease	MIM Number	Chromosome	Gene	Mutation (Common Name)	Mutation (HGVS Name)	Reference Cluster ID	Group	Mutation Detected in 25 Exomes
Restrictive dermopathy	275210	1	*ZMPSTE24*	c.1085dupT	NM_005857.3: c.1078dupT	rs137854889	3	no
					NP_005848.2: p.Cys359_Phe360?fs			
Joubert syndrome	614424	2	*TMEM237*	R18X	NM_001044385.1: c.52C>T	rs199469707	2	yes
					NP_001037850.1: p.Arg18Ter			
Sitosterolemia	210250	2	*ABCG8*	S107X	NM_022437.2: c.320C>G	rs137854891	2	yes
					NP_071882.1: p.Ser107Ter			
Dilated cardiomyopathy with ataxia syndrome	610198	3	*DNAJC19*	IVS3-1G>C	NM_145261.3: c.130-1G>C	rs137854888	2	yes
Spinal muscular atrophy type III	253400	5	*SMN1*	exon 7 del	N/A	N/A	1	no
Cystic fibrosis	219700	7	*CFTR*	F508del	NM_000492.3: c.1521_1523delCTT	rs113993960	1	no
					NP_000483.3: p.Ile507_Phe508?			
				M1101K	NM_000492.3: c.3302T>A	rs36210737	1	yes
					NP_000483.3: p.Met1101Lys			
Limb girdle muscular dystrophy 2H	254110	9	*TRIM32*	D487N	NM_001099679.1: c.1459G>A	rs111033570	2	yes
					NP_001093149.1: p.Asp487Asn			
Usher syndrome type 1F	602083	10	*PCDH15*	c.1471delT	NM_001142763.1: c.1101delT	rs199469706	2	yes
					NP_001136235.1: p.Leu368fs*			
Oculocutaneous albinism type 1A	203100	11	*TYR*	C91Y	NM_000372.4: c.272G>A	rs137854890	3	yes
					NP_000363.1: p.Cys91Tyr			
Nonsyndromic deafness	220290	13	*GJB2*	c.35delG	NM_004004.5: c.35delG	rs80338939	3	no
					NP_003995.2: p.Gly12Valfs			
Bardet-Biedl syndrome	209900	16	*BBS2*	IVS3-2A>G	NM_031885.3: c.472-2A>G	rs137854887	2	yes
Limb girdle muscular dystrophy 2I	607155	19	*FKRP*	L276I	NM_024301.4: c.826C>A	rs28937900	1	yes
					NP_077277.1: p.Leu276Ile			
Nonsyndromic mental retardation	614020	19	*TECR*	P182L	NM_138501.5: c.545C>T	rs199469705	1	yes
					NP_612510.1: p.Pro182Leu			

This table is ordered by chromosome. Group 1 mutations correspond to diseases that were either previously observed or reported[22–24] to have occurred in study subjects or their children. Group 2 mutations were previously reported in the Hutterites[25–32] and were present in the exome sequences of 25 Hutterites. Group 3 mutations were discovered in our laboratory during the course of this study. Both the "common" mutation names, as well as HGVS names, are provided; in some cases, the coding sequence has been revised since the original mutation publication because the common name is outdated. We use the common names throughout this manuscript to retain consistency with existing literature on these mutations.

Table 2. Results of Carrier Screening for 14 AR Mutations in 1,644 Hutterites from South Dakota

Disease	Gene Mutation	Number of Heterozygotes	Number of Homozygotes	Number Screened	Carrier Frequency in Hutterites	Carrier Frequency in Other Populations
Limb girdle muscular dystrophy 2H	*TRIM32* p.Asp487Asn	228	9	1,493	0.153 (1 in 6.5)	unknown (only two non-Hutterite cases reported[42])
Oculocutaneous albinism type 1A	*TYR* p.Cys91Tyr	180	3	1,281	0.141 (1 in 7)	private mutation
Spinal muscular atrophy type III	*SMN1* exon 7 del	179	2	1,415	0.127 (1 in 8)	1 in 35[43]
Limb girdle muscular dystrophy 2I	*FKRP* p.Leu276Ile	121	3	1,127	0.107 (1 in 9.5)	1 in 300[44]
Sitosterolemia	*ABCG8* p.Ser107Ter	127	4	1,515	0.084 (1 in 12)	private mutation
Joubert syndrome	*TMEM237* p.Arg18Ter	122	0	1,520	0.080 (1 in 12.5)	private mutation
Cystic fibrosis	*CFTR* p.Met1101Lys	108	6	1,473	0.073 (1 in 13.5)	unknown (only one non-Hutterite case reported[41])
Nonsyndromic mental retardation	*TECR* p.Pro182Leu	103	5	1,496	0.069 (1 in 14.5)	private mutation
Restrictive dermopathy	*ZMPSTE24* c.1085dupT	87	0	1,361	0.064 (1 in 15.5)	unknown (<60 cases worldwide[45])
Nonsyndromic deafness	*GJB2* c.35delG	54	0	1,510	0.036 (1 in 28)	1 in 40[35]
Dilated cardiomyopathy with ataxia syndrome	*DNAJC19* IVS3-1G>C	42	0	1,504	0.028 (1 in 36)	private mutation
Bardet-Biedl syndrome	*BBS2* IVS3-2A>G	42	0	1,518	0.028 (1 in 36)	private mutation
Usher syndrome type 1F	*PCDH15* c.1471delT	38	0	1,524	0.025 (1 in 40)	private mutation
Cystic fibrosis	*CFTR* p.Phe508del	32	0	1,482	0.022 (1 in 45.5)	1 in 30[46]

This table is ordered by carrier frequency. The combined carrier frequency for cystic fibrosis (c.1521_1523delCTT + c.3302T>A) is 0.093 (1 in 11). We use common mutation names to retain consistency with the existing literature.

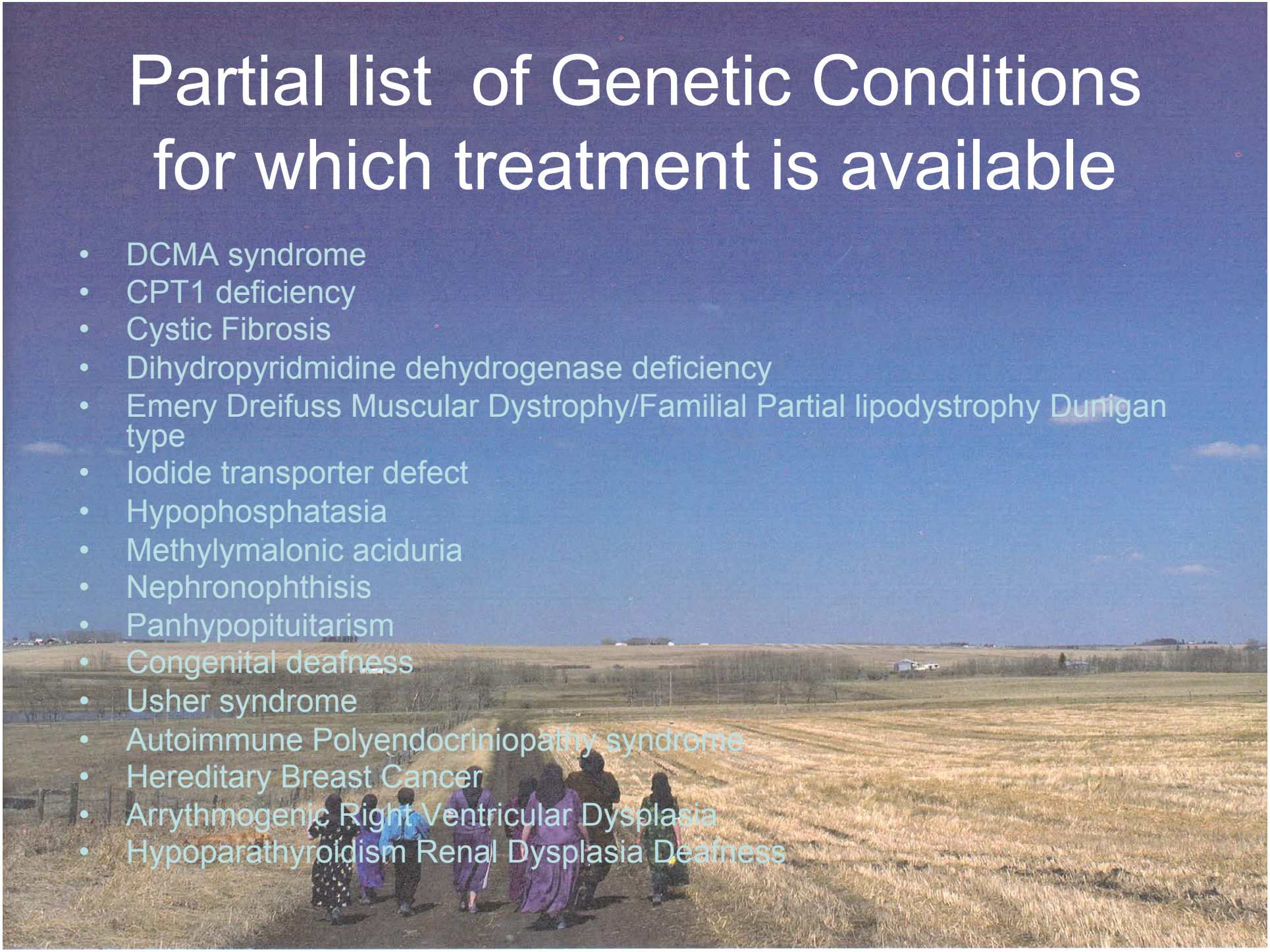
Range TRIM32/LGMD2H 1/6.5 to dF508 1/45.5
SMA SMN del exon 7: 1/8 versus 1/35
LGMD2I FKRP L276I : 1/9.5 versus 1/300
Deafness GJB2 del35G: 1/28 versus 1/40
CF CFTR dF508 1/45.5 versus 1/30

Hutterite Carrier Chip

Development of a Diagnostic Chip for the Hutterite Population

TL Dyck[1], B Triggs-Raine[2], CR Greenberg[2,3], C Ober[4], JS Parboosingh[5], AM Innes[5], B Gerull[6], K Boycott[7], EL Spriggs[1,2] [1]Clinical Biochemistry and Genetics, Diagnostic Services of Manitoba, Winnipeg, Manitoba, Canada, [2]Departments of Biochemistry & Medical Genetics and Pediatrics & Child Health, University of Manitoba, Winnipeg, Manitoba, Canada, [3]Child Health Program, Winnipeg Regional Health Authority, Winnipeg, Manitoba, Canada, [4]Department of Human Genetics, University of Chicago, Chicago, Illinois, United States, [5]Department of Medical Genetics, University of Calgary, Calgary, Alberta, Canada, [6]Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada, [7]Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Partial list of Genetic Conditions for which treatment is available



- DCMA syndrome
- CPT1 deficiency
- Cystic Fibrosis
- Dihydropyridmidine dehydrogenase deficiency
- Emery Dreifuss Muscular Dystrophy/Familial Partial lipodystrophy Dunigan type
- Iodide transporter defect
- Hypophosphatasia
- Methylymalonic aciduria
- Nephronophthisis
- Panhypopituitarism
- Congenital deafness
- Usher syndrome
- Autoimmune Polyendocriniopathy syndrome
- Hereditary Breast Cancer
- Arrythmogenic Right Ventricular Dysplasia
- Hypoparathyroidism Renal Dysplasia Deafness

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