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SOCIAL EVENTS

THURSDAY, MAY 4

Welcome Reception
1830–2100
Saveur Room, Hyatt Regency Hotel
Tickets: No charge for registered delegates; $50 for guests

FRIDAY, MAY 5

Garrod Symposium Gala Dinner & Pioneer Award Presentation
1830–2200
McCord Museum
Tickets: $125.00 per person
Meet in the Hyatt Regency Hotel lobby at 1810 to walk over.

The McCord Museum is a public research and teaching museum dedicated to the preservation, study, diffusion, and appreciation of Canadian history. The museum, whose full name is McCord Museum of Canadian History, is located at 690 Sherbrooke Street West, next to McGill University, in downtown Montreal.

BUSINESS MEETINGS

THURSDAY, MAY 4

1300–1500	CIMDRN (Invitation Only) Canadian Inherited Metabolic Diseases Research Network	Creation Room
1300–1500	Dietitians' Webinar	Symphonie 2A
1300–1500	Nurses' Session	Symphonie 2B
1700–1830	Garrod Executive Committee Meeting (invitation only)	Symphonie 5

SATURDAY, MAY 6

1230–1330	Garrod Association Membership Meeting (with lunch)	Ovation Room

REGISTRATION DESK HOURS

The Registration desk is located in the Inspiration Foyer. The desk will be open:

Thursday, May 4	1000–1900
Friday, May 5	0700–1800
Saturday, May 6	0700–1200

SCHEDULE AT A GLANCE

THURSDAY MAY 4		**ROOM**
1300–1500	Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)	Creation
1300–1500	Dietitians' Webinar	Symphonie 2A
1300–1500	Nurses' Session	Symphonie 2B
1700–1830	Garrod Executive Committee Meeting (invitation only)	Symphonie 5
1830–2100	Welcome Reception	Saveur

FRIDAY MAY 5		
0645–0750	Breakfast	Inspiration
0800–0955	Bone Involvement in Metabolic Diseases	Ovation
0955–1025	Refreshment Break and Poster Viewing	Inspiration
1025–1200	Bone Involvement in Metabolic Diseases continued	Ovation
1200–1300	Lunch	Inspiration
1310–1455	Treatment of Metabolic Disorders	Ovation
1455–1525	Refreshment Break and Poster Viewing	Inspiration
1525–1635	Treatment of Metabolic Disorders continued	Ovation
1635–1745	Cocktails and Poster Viewing	Inspiration
1830–2200	Garrod Symposium Gala Dinner and Pioneer Award Presentation at McCord Museum	Offsite
	Meet in the Hyatt Regency Hotel lobby at 1810 to walk over	

SATURDAY MAY 6		
0645–0750	Breakfast	Inspiration
0800–0935	Leukodystrophies	Ovation
0935–1005	Refreshment Break and Poster Viewing	Inspiration
1005–1145	Leukodystrophies continued	Ovation
1200–1330	Lunch	Ovation
1230–1330	Garrod Association Membership Meeting	Ovation

POSTER PRESENTATIONS

Posters can be mounted on Friday morning between 0800–0900. Posters are located in the exhibit area, and can viewed during all breaks. The Poster Walk will take place on Friday afternoon at 1635–1745, and presenters will be attending their posters at that time.

THURSDAY MAY 4

1300–1500 | CIMDRN BUSINESS MEETING

Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)

Time 1300–1500
Room Creation

1300–1500 | NURSES' SESSION

Time 1300–1500
Room Symphonie 2B

1300–1500 | DIETITIANS' WEBINAR

Time 1300–1500
Room Symphonie 2A

Moderators **Manon Bouchard** Dt.P., CHU Sainte-Justine, génétique médicale
Marie Lefrançois Dt.P. / R.D., McGill University Health Center, Montreal Children's Hospital

1300–1400 **Mitochondrial Disease: A Dietary and Nutritional Perspective**
Mark Korson, Genetic Metabolic Center for Education, Salem

Objectives At the end of this session, participants will be able to:
- Discuss mitochondrial autonomic dysfunction and how it impacts the gut.
- Develop an approach for managing the nutritional needs of patients with GI dysmotility.
- Describe the unique nutritional approach for select mitochondrial diseases, e.g., PDHC deficiency.

1400–1500 **Dietary Treatment of Cobalamin C Deficiency**
Can Ficicioglu, The Childeren's Hospital of Philadelphia

Objectives At the end of this session, participants will be able to:
- Recognize: Biochemistry, Genetics, Clinical manifestations, Diagnosis, Basic principles of Treatment of Cobalamin C disease.
- Discuss: If there is a relationship between initial or long-term metabolic control and neurocognitive outcomes.
- Discuss: If dietary protein composition affects long-term metabolic control or amino acid imbalances.
- Discuss: If the long-term protein composition of the diet affects growth or neurocognitive outcomes.

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1700–1830 | GARROD EXECUTIVE BOARD BUSINESS MEETING

Time 1700–1830
Room Symphonie 5

WELCOME RECEPTION | 1830–2100

All attendees are welcome to attend.
Saveur Room at the Hyatt Regency Hotel

FRIDAY MAY 5 MORNING | 0645–1300

0645–0750 | BREAKFAST

Time 0645–0750
Room Inspiration

0800–1200 | PLENARY SESSION: BONE INVOLVEMENT IN METABOLIC DISEASES

Time 0800–0815
Room Ovation

Welcome Remarks
Pierre Allard, 2017 Garrod Symposium Chair

Time 0815–1200
BONE INVOLVEMENT IN METABOLIC DISEASES

Moderator **Philippe Campeau**, Université de Montréal

0815-0850 **Skeletal Manifestations of Inborn Errors of Metabolism: Lessons form Congenital Disorders of Glycosilation**
Roberto Mendoza-Londono, University of Toronto, The Hospital for Sick Children

Objectives At the end of this session the participant will be able to:
- Discuss the basic elements of bone formation and maintenance.
- List the common clinical and radiological features of skeletal dysplasias.
- Identify the specific skeletal changes that can be seen in Congenital Disorders of Glycosylation.
- Compare the skeletal manifestations of the most common forms of inborn errors of metabolism.

0850-0925 **Bone mineralization gone wrong: Defective enzymatic processing of mineralization inhibitors in osteomalacia (hypophosphatasia and X-linked hypophosphatemia)**
Marc McKee, McGill University, Shriners Hospital for Children

Objectives At the end of this session the participant will be able to:
- List several molecular determinants of skeletal and dental mineralization that act directly on the mineral phase.
- Explain how pyrophosphate and tissue-nonspecific alkaline phosphatase function in hypophosphatasia.
- Explain how osteopontin and PHEX functions in X-linked hypophosphatemia.
- Discuss the balance between mineralization inhibitor action and the enzymes that degrade them.

0925-0955 **Discussion**

0955-1025 **Refreshment Break, Exhibits, and Poster Viewing**, Inspiration Room

1025-1100 **Everything is Metabolism – Also in the Skeleton**
Philippe Campeau, Université de Montréal

Objectives At the end of this session the participant will be able to:
- Identify metabolic processes associated with the skeleton as an organ.
- Identify examples of bone disease associated with metabolic disorders.
- Identify bone disorders associated with metabolic processes intrinsic to the skeletal system.

1100-1130 **Platform Presentations of Selected Abstracts**

1100-1115 **Second family with Mabry Syndrome caused by PIGL mutation**
Ruqaiah S Altassan, Montreal Children's Hospital, McGill University Health Center, Montreal.

1115-1130 **A viable mouse model of severe mitochondrial disease: adipose-specific fumarate hydratase deficiency**
Hao Yang, Université de Montréal and CHU Sainte-Justine.

1130-1200 Discussion

1200–1300 | LUNCH, Inspiration Room

FRIDAY MAY 5 AFTERNOON | 1310–1745

1310–1635 | PLENARY SESSION: TREATMENT OF METABOLIC DISORDERS

Time	1310–1635
Room	Ovation
Moderators	**Catherine Brunel-Guitton**, Université de Montréal, CHU Sainte-Justine **Grant Mitchell**, Université de Montréal, CHU Sainte-Justine
1310-1315	**Introductions**
1315-1350	**Clinical diagnosis and treatment of disorders of cobalamin metabolism** **Carlo Dionisi Vici**, Bambino Gesù Children's Hospital, Rome
Objectives	At the end of this session the participant will be able to: • Recognize the clinical signs of cblC and other defects of cobalamin metabolism. • Diagnose a patient with cblC and other defects of cobalamin metabolism. • Discuss about treatment in patients with cblC and other defects of cobalamin metabolism.
1350-1425	**Surprises from the study of patients with inherited disorders of one-carbon metabolism** **David Rosenblatt**, McGill University
Objectives	At the end of this session the participant will be able to: • List two disorders that are phenocopies of cblC. • Compare disorders of cobalamin metabolism. • Explain how mutations in transcription factors can result in an inborn error of cobalamin metabolism.
1425-1455	**Discussion**
1455-1525	**Refreshment Break, Exhibits, and Poster Viewing**, Inspiration Room
1525-1600	**Metabolic Pathway Reprogramming: A Novel Therapeutic Approach for Tyrosinemia Type I** **Karl-Dimiter Bissig**, Baylor College of Medicine, Houston
Objectives	At the end of this session the participant will be able to: • Explain current therapy of tyrosinemia type I. • Compare current therapy to experimental therapy. • Summarize metabolic pathway reprogramming.
1600-1615	**Platform Presentation of Selected Abstract**
	Disorders of intracellular cobalamin metabolism: phenotype, genotype and long-term treatment outcome Lizbeth Mellin-Sanchez, University of Toronto, Toronto.
1615-1635	Discussion

COCKTAILS AND POSTER WALK | 1635–1745

Inspiration Room

(all presenters to attend their posters)

GALA RECEPTION AND BANQUET | 1830–2200

McCord Museum

Meet in the Hyatt Hotel Lobby at 1810 to walk over.

Tickets: $125 per person, includes museum exhibits, reception, dinner, and gratuities.

GARROD 2017 AWARD PRESENTATION

The Garrod 2017 Pioneer Award will be presented to Dr. Charles Scriver

SATURDAY MAY 6 MORNING | 0645–1330

0645–0750 | BREAKFAST

Time 0645–0750
Room Inspiration

0800–1145 | PLENARY SESSION: LEUKODYSTROPHIES

Time 0800–1145
Room Ovation

Moderators **Geneviève Bernard**, McGill University, Montreal Children's Hospital
John Mitchell, McGill University, Montreal Children's Hospital

0800-0810 **Introductions**

0810-0900 **POLR3-related leukodystrophy: from gene identification and phenotypic description to understanding of disease mechanisms**
Geneviève Bernard, McGill University, Montreal Children's Hospital

Objectives At the end of this session the participant will be able to:
- List the clinical manifestations of POLR3-related leukodystrophy.
- Summarize the MRI characteristics of the disease.
- Discuss the genetic causes of the disease, and what is known on the pathophysiology.

0900-0915 **Platform Presentation of Selected Abstract**

Expanding the phenotypic spectrum of POLR3-related leukodystrophy
Laurence Gauquelin MD, Stefanie Perrier BSc, McGill University Health Center, Montreal, Canada.

0915-0935 Discussion

0935-1005 **Refreshment Break, Exhibits, and Poster Viewing**, Inspiration Room

1005-1050 **Metachromatic leukodystrophy: New insights into treatment**
Nicole Wolf, VU University Medical Center, Amsterdam

Objectives At the end of this session the participant will be able to:
- List the different forms of MLD and their respective symptoms.
- Discuss indications for hematopoietic cell transplantation.
- Summarize supportive treatment options for MLD patients.

1050-1105 **Platform Presentation of Selected Abstract**

The application of a magnetic resonance imaging algorithm in the clinical diagnosis of white matter abnormalities
Ravi Datarg BMSc, Western University, London, ON.

1105-1135 **Discussion**

1135-1145 **Wrap-up and Closing Remarks**

1200–1330 | LUNCH AND GARROD ASSOCIATION MEMBERSHIP MEETING, Ovation Room

Time 1230–1330
Room Ovation Room

ABSTRACTS

PLATFORM PRESENTATIONS

Friday, May 5, 1100-1115

Second family with Mabry Syndrome caused by *PIGL* mutation

Ruqaiah S Altassan[a], Chantal Poulin[b], Daniela Buhas[a,c,*]
[a]Department of Medical Genetics, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada. [b]Department of Pediatric Neurology, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada. [c]Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
[*]Corresponding author.

Objectives: To describe the second family with Mabry syndrome (*H*yper*p*hosphatasia *mental retardation syndrome-HPRMS) caused by PIGL mutation.*

Design and Methods: Clinical evaluation and molecular testing of two siblings presented to our institution with distinctive facial features, developmental delay, mental retardation, seizure disorder, skeletal deformities, and high alkaline phosphatase.

Results: Molecular testing for the index case showed two heterozygous mutations in PIGL gene (C.60G>A; p.TRP20*, and c.262C>T; p.ARG88Cys). Segregation analysis confirmed compound heterozygous inheritance of the two alleles. Same changes found in the other affected sibling.

To date, six mutations in PIGL gene have been identified in seven patients presenting with CHIME syndrome (*c*oloboma, *h*eart defect, early-onset *i*chthyosiform dermatosis, *m*ental retardation and *e*ar anomalies /hearing loss alternate with *e*pilepsy) and only one patient with Mabry phenotype (Am J Med Genet A.2015Apr:167A(4):777-85). In our patients, some of the clinical features overlap between CHIME and Mabry syndrome especially the CNS involvement; however, they do not have coloboma, heart defect or hearing impairment. The distinctive skeletal phenotype of short terminal phalanges and the high alkaline phosphatase diverged our diagnosis to Mabry syndrome.

Conclusions: Our clinical, biochemical and molecular findings support the previous report of Mabry syndrome caused by *PIGL* mutation, which is another Phosphatidylinositol Glycan (PIG) anchor biosynthesis class that should be considered in the differential diagnosis of the known PIG classes *(PIGV, PIGO, and PIGW)* and the Post GPI Attachment to Proteins genes *(PGAP2, PGAP3)* that are currently linked to Mabry syndrome.

Keywords: *H*yper*p*hosphatasia *m*ental *r*etardation *s*yndrome (HPMRS), Mabry syndrome, *PIGL* gene, CHIME syndrome, autosomal recessive intellectual disability.

Friday, May 5, 1115-1130

A viable mouse model of severe mitochondrial disease: adipose-specific fumarate hydratase deficiency

Hao Yang[1], Shupei Wang[1], Pierre Allard[1], Catherine Brunel-Guitton[1], Saverio Cinti[2], and Grant A. Mitchell[1].
[1]Division of Medical Genetics, Department of Pediatrics, Université de Montréal and CHU Sainte-Justine. [2]Department of Experimental and Clinical Medicine, Center of Obesity, United Hospitals, University of Ancona, Ancona, Italy.

Objective: To obtain a viable animal model of severe mitochondrial disease (MD). The disease-causing potential of mutations in many mitochondrial proteins is unknown and poses a major challenge for interpreting genomic data. A corresponding animal model would be useful to understand the biological impact of mutations. We hypothesized that mice with severe mitochondrial disease only in fat tissues would be viable and would allow evaluation of tissues with high and low energy utilization: brown and white adipose tissues (BAT and WAT), respectively. We tested this with the Krebs cycle enzyme fumarate hydratase (FH). Systemic FH deficiency is clinically severe in humans and embryonically lethal in mice.

Method: We created adipose tissue-specific FH knockout (AFHKO) mice using adipocyte-specific Cre-mediated excision driven by the adiponectin promoter.

Results: AFHKO mice survived despite having severe mitochondrial dysfunction. ATP content was low: in BAT (3.5% of control content, $p<0.001$) and WAT (30.4%, $p<0.01$), with swollen mitochondria and disrupted cristae. Krebs cycle metabolite profiles were abnormal in AFHKO BAT and WAT, with low acetyl- and succinyl-CoA and high succinate and fumarate. AFHKO mice have distinct, easily-measurable phenotypes: cold-sensitivity, leanness, small white adipocytes (modal diameter, 5-mo-old AFHKO 50µm vs controls, 70µm). Brown AFHKO adipocytes were monovesicular and hypertrophic. AFHKO BAT mass was 1.4-fold higher than controls. 10-mo-old AFHKO mice were insulin sensitive and glucose tolerant.

Conclusion: AFHKO mice provide proof of principal that an adipose knockout can permit study of the biological effects of mutations and possibly treatment for a severe MD.

Keywords: mitochondrial disease, adipose tissue, animal model, FH deficiency

Friday, May 5, 1600-1615

Disorders of intracellular cobalamin metabolism: phenotype, genotype and long-term treatment outcome

Lizbeth Mellin-Sanchez[1], Garrett Bullivant[1], Vivian Cruz[1], Julian Raiman[2], Andreas Schulze[1,3], Komudi Siriwardena[4], Saadet Mercimek-Mahmutoglu[1,3].
[1]Division of Clinical and Metabolic Genetics, Department of Pediatrics, University of Toronto, Toronto. [2]Birmingham's Children Hospital, Birmingham, England. [3]Genetics and Genome Biology Program, Research Institute, The Hospital for Sick Children, Toronto, Canada. [4]Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada

Objective: To determine the phenotype, genotype, and treatment outcome of all patients with disorders of intracellular cobalamin (cbl) metabolism and to compare the treatment outcome of patients diagnosed by newborn screening (NBS) and symptomatically, we performed a retrospective cohort study.

Background: Disorders of intracellular cobalamin (cbl) metabolism are the result of defects in the synthesis of metabolically active coenzymes including methylcobalamin and adenosylcobalamin from dietary cobalamin. These disorders are grouped into: A, B, C, D, D1, D2, E, F, G, J.

Methods: All patients were included. Electronic charts were reviewed. We compared treatment outcome of patients identified by NBS versus symptomatically.

Results: There were 33 patients: 26 cblC, 3 cblG, 2 cblE, one cblD1 and one cblB. Sixteen patients were identified by newborn screen. Twenty-five patients had developmental delay and 11 patients had seizures. Brain magnetic resonance imaging (MRI) revealed cerebral atrophy in 10 patients. Developmental delay was present in 69% of patients identified by NBS versus 82% of symptomatic patients. Seizures were present in 19% of the patients identified by NBS versus 47% of symptomatic patients. Cerebral atrophy in brain MRI was present in 6% of the patients identified by newborn screening versus 53% of symptomatic patients. All patients were treated with daily intramuscular hydroxcobalamin (dose 0.5-10mg) and/or betaine and/or l-carnitine.

Conclusion: We report 33 new patients with disorders of intracellular cbl metabolism s retrospective cohort study. cblC was the most common subtype. Patients identified by newborn screening and treatment started in the neonatal period appear to have better neurodevelopmental outcome.

Keywords: Cobalamin, New born screening, homocystinuria, methylmalonic aciduria

Saturday, May 6, 0900-0915

Expanding the phenotypic spectrum of POLR3-related leukodystrophy

Laurence Gauquelin MD[1], Stefanie Perrier BSc[1,2], Luan T. Tran MSc[1,2], Kether Guerrero MSc[1,2], Norberto Rodriguez Espinosa MD[3], Ingrid Tejera Martin MD[4], Nicole I. Wolf MD PhD[5], Daniela Pohl MD PhD[6], Savithri Nageswaran MBBS MPH[7], Annette E. Grefe MD[8], Genevieve Bernard MD MSc FRCPC[1,2,9].

[1]Department of Neurology and Neurosurgery, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Center, Montreal, Canada. [2]Child Health and Human Development Program, Research Institute of the McGill University Health Center, Montreal, Canada. [3]Unidad de Neurologia de la Conducta y Memoria, Hospital Universitario Nuestra Sra De Candelaria, Santa Cruz de Tenerife, Canary Islands, Spain. [4]Neurologia, Hospital Quironsalud Tenerife, Santa Cruz de Tenerife, Canary Islands, Spain. [5]Department of Child Neurology, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands. [6]Department of Neurology, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Canada. [7]Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America. [8]Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America. [9]Department of Medical Genetics, Montreal Children's Hospital, McGill University Health Center, Montreal, Canada.

Background: RNA polymerase III-related leukodystrophy (POLR3-HLD) is the second most common hypomyelinating leukodystrophy and is caused by recessive mutations in *POLR3A, POLR3B* and *POLR1C*.

Objective: To describe the extremes of the clinical and magnetic resonance imaging (MRI) phenotypic spectrum of POLR3-HLD.

Methods: A retrospective chart review of five mutations proven patients with very atypical phenotypes: 2 infants with very severe clinical features and 3 adults with an extremely mild phenotype.

Results: Patients 1 and 2 presented within the first months of life with failure to thrive and developmental delay and regression. They died before 18 months of age from respiratory failure. Their MRI did not reveal the typical characteristics of POLR3-HLD. Both patients had a combination of a pathogenic variant leading to a premature stop codon in *POLR3A* (patient 1 c.2119C>T, p.Q707* and patient 2 c.1681C>T, p.R561*), as well as an intronic variant leading to aberrant splicing: c.1771-7C>G. Patients 3 and 4 were adult siblings with severe myopia who were diagnosed with hypomyelination on MRI performed for an unrelated reason. Their MRI pattern was typical for POLR3-HLD but with more residual myelin than typically seen. Patient 5 is an adult with an extremely mild phenotype who was diagnosed in the context of affected offsprings. These three patients are homozygous for the common *POLR3B* mutation (c.1568T>A, p.Val523Glu).

Conclusions: These findings are a good illustration of the expansion of a known phenotype in the era of next generation sequencing. At both ends of the spectrum, genotype-phenotype correlation is present.

Keywords: POLR3-related leukodystrophy, 4H leukodystrophy, hypomyelination, magnetic resonance imaging (MRI).

Funding Acknowledgement: GB has received a Research Scholar Junior 1 award from the Fonds de Recherche du Québec en Santé (FRQS) 2012-2016 and a Canadian Institute of Health Research New Investigator salary award (2017-2022) (201512MSH-360766-171036). This work was supported by operating grants from Réseau de Médecine Génétique Appliquée of the FRQS. SP is supported by the Max Stern recruitment fellowship from McGill University.

Saturday, May 6, 1050-1105

The application of a magnetic resonance imaging algorithm in the clinical diagnosis of white matter abnormalities

Ravi Datarg BMSc[g], Asuri N. Prasad MBBS MD FRCPC FRCPE[c,d,f], Keng Y. Tay MBBS BSc FRCPR[b], Charles A. Rupar PhD FCCMG[a,d,e,f], Pavlo Ohorodnyk MD[b], Michael Miller PhD[d,f], Chitra Prasad MD FRCPC FCCMG FACMG[d,f]. Departments of [a]Biochemistry, [b]Medical Imaging, [c]Neurology, [d]Paediatrics, [e]Pathology and Laboratory Medicine, London Health Sciences Centre, London, ON. [f]Children's Health Research Institute, London, ON. [g]Western University, London, ON.

Background: White matter abnormalities (WMA) reported on cranial magnetic resonance imaging (MRI) often pose a diagnostic challenge when trying to establish an etiologic diagnosis. During childhood and adult years, genetic and metabolic disorders in addition to acquired conditions are included in differential diagnoses. To help clinicians and radiologists, a structured algorithmic has been recommended to aid in establishing working diagnoses that will facilitate appropriate biochemical and genetic investigations.

Objective: This retrospective pilot study investigated the validity and diagnostic utility of such an algorithm for patients seen in our clinics.

Methods: The MRI algorithm was applied to thirty-one patients selected at random from patients attending the neurogenetic and neurometabolic clinic at a tertiary care hospital. These patients varied in age from 5 months to 79 years old, and presented confirmed white matter signal abnormalities (WMSAs) on cranial MRIs. Twenty-one patients had a confirmed biochemical genetic diagnosis and 10 patients had confirmed non-specific WMA diagnoses (etiology unknown). Two radiologists, blinded to confirmed diagnoses, used patient MRI scans and clinical abstractions to classify possible WMA diagnoses through utilizing the algorithm.

Results: The MRI algorithm displayed a sensitivity of 100%, a specificity of 30.0% and a positive predicted value of 74.5%. Cohen's kappa statistic for inter-radiologist agreement was 0.733, suggesting "good" agreement between radiologists.

Conclusions: Although a high diagnostic utility was not observed, results suggest that this MRI algorithm has promise as a clinical tool for clinicians and radiologists. This study has identified various benefits and limitations of this approach for future directions.

Keywords: white matter abnormalities, myelination, magnetic resonance imaging, diagnostic utility, diagnostic neuroradiology

POSTER PRESENTATIONS
Friday, May 5, 1730–1830

P101 Case Report: Two pregnancies in a patient with maple syrup urine disease

Shailly Jain-Ghai MD[a], Melissa Sheehan RD[b], Komudi Siriwardena MD[a], and Alicia Chan MD[a]
[a]Department of Medical Genetics, University of Alberta and Stollery Children's Hospital, Edmonton, Alberta. [b]Nutrition Services, Alberta Health Services; Stollery Children's Hospital, Edmonton, AB.

Maple syrup urine disease (MSUD) is an autosomal recessive disorder with deficiency of branched-chain alpha-ketoacid dehydrogenase. Mainstay of treatment revolves around dietary restriction of branch chain amino acids. With improved dietary management, female patients are surviving into reproductive years. Management of pregnant patients with inborn errors of metabolism is being reported more frequently but remains challenging. Here, we describe the course of one patient with MSUD through two pregnancies.

The patient was diagnosed with MSUD at 7 days of age with leucine (Leu) greater than 3500 umol/L. Although her MSUD control was stable for many years, pre-conception control was poor with Leu between 600-700 umol/L. During her first trimester of first pregnancy, she required multiple hospitalizations due to metabolic decompensations precipitated by nausea, vomiting as well as food insecurity. With strict dietary management which included increasing the metabolic protein along with gradual increases in natural protein, Leu levels stabilized. Specialized metabolic protocols were created for labour and delivery and nutrition post-partum. Patient did not have metabolic decompensations during or after delivery. Similar management was followed during her second pregnancy. During the second post-partum period, patient presented with a severe decompensation with encephalopathy. This was in conjunction with a urinary tract infection. Leu reached a peak of 1140 umol/L.

In summary, we present two pregnancies in one MSUD patient. We outline dietary management through different trimesters, labour and delivery, and post-partum. The case highlights potential high-risk periods for metabolic decompensation during pregnancy and post-partum in MSUD patients. Close monitoring remains crucial. Both children, oldest one at 3 years of age, are showing normal early development and growth.

P102 Characterization of 5 adult patients with m.15152G>A, a novel mutation in mitochondrial cytochrome b

Natascia Anastasio[a], John Mitchell[a], and Yannis Trakadis[a]
[a]Department of Medical Genetics, McGill University Health Center, Montreal, QC.

Objectives: Mutations in mitochondrially-encoded cytochrome b, *MT-CYB*, are one of the most common causes of CIII deficiency and this disorder has huge phenotypic variability (FEBS J 2005;272:3583-3592.). We present a case of familial CIII deficiency and characterize the variability of symptoms in adult patients.

Method: Clinical phenotyping, mitochondrial DNA familial variant testing and heteroplasmy analysis, muscle biopsy.

Results: The proband and his sister presented in childhood with recurrent episodes of ketotic hypoglycemia, decreased endurance, leg cramps and gastrointestinal dysmotility. Both were found to be homoplasmic for an m.15152G>A (p.G136S) mutation in *MT-CYB*. They have had good response to coenzyme Q10. Their mother was also found to be homoplasmic and showed findings in different organ systems, as is typical of a mitochondrial disorder. These include neurological, muscular, psychiatric, gastrointestinal, cardiovascular, auditory, and visual symptoms. These findings were similar to those described by 4 other adult family members; all heteroplasmic for the familial *MT-CYB* mutation. Three of five patients had abnormal muscle biopsies which showed ragged red fibers (1/3), myopathic changes (2/3) and mitochondrial proliferation (1/3). Two of five adult patients were treated with coQ10 and showed subjective improvement.

Conclusions: This is the first report of the m.15152G>A mutation in *MT-CYB* causing mitochondrial disease. Our case highlights the phenotypic variability in symptoms, even amongst patients with the same mutation. Our case also raises the possibility of response to treatment with coenzyme Q10. Future directions include muscle mtDNA heteroplasmy testing, blue native stain and respiratory chain enzyme analysis to further characterize the phenotype.

Keywords: mitochondrial, respiratory chain, MT-CYB, myopathy

P103 Challenges in detecting methylmalonic acidemia on newborn screening using an underivatized tandem mass spectrometry (MS/MS) method

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Newborns born in the province of Alberta are screened for 17 primary disorders including methylmalonic acidemias and acidemias associated with elevated C5OH. In 2015, our newborn screening (NBS) laboratory switched from a derivitized to an underivatized MS/MS method. One of the known limitations of the underivatized method is the inability to distinguish isobaric compounds C4DC (i.e., succinyl-/methylmalonyl-) from C5OH (i.e., 3-hydroxyisovaleryl-/3-Hydroxy-2-methyl-) carnitines. Here we report an infant with methylmalonic acidemia detected based on a false positive NBS screen for elevated C5OH. The NBS results showed an elevated C5OH+C4DC level and C5DC+C6OH/C8 ratio, resulting in a borderline abnormal result that was flagged, triggering a recollection. Both C3 and C6DC levels were normal. The second sample was collected at 14 days old with similar results and the screen was called out as a positive C5OH screen. Follow-up plasma AC profile at 24 days old showed 1.9-fold elevation of C3 and C4DC; however, C5OH was normal. Plasma methylmalonic acid (MMA) levels were 7.5-fold elevated (1.5 umol/L; Normal: 0.04-0.2 umol/L), while plasma total homocysteine was normal. Given this patient's unexplained elevated MMA level, a next generation sequencing gene panel for methylmalonic acidemias was performed and a novel homozygous variant in the SUCLA2 gene was found; c.1340T>G (p.Val447Gly), predicted to be damaging.

The present patient illustrates the challenge of detecting infants with alternate causes of elevated MMA on NBS using an underivatized MS/MS method.

Keywords: 1. methylmalonic academia, 2. underivatized, 3. tandem mass spectrometry, 4. SUCLA2, 5. newborn screening

P104 Variable expressivity within one family affected with *FBXL4* mutation

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Objectives: To explore the phenotypic heterogeneity of mitochondrial depletion syndrome13 within one family.

Design and Methods: We present the clinical and biochemical phenotypes of two siblings affected with mitochondrial depletion syndrome 13.

Results: Nuclear mitochondrial exome sequencing showed two novel mutations in *FBXL4* gene (c.526T>C; p.Trp176Arg and c.486T>A; p.Tyr162Ter). Segregation analysis confirmed compound heterozygous inheritance of the two alleles.

Conclusion: Mitochondrial depletion syndrome 13 has been recently linked to mutation in F-box leucine rich repeat protein 4 *(FBXL4)* genes. The predominant phenotypes in all 31 reported patients are early onset encephalopathy, hypotonia, severe global developmental delay and lactic acidosis.

Our patients presented with isolated early neonatal feeding intolerance, necessitating TPN for more than five years (older sibling, now seven years old) and still ongoing (for the youngest one, now 17-

month old). They also have neutropenia with recurrent infections and episodic mild lactic acidosis. The CNS involvement was only present in the younger sibling, who manifested mild motor delay and Leigh-like disease in the brain MRI.
Phenotypic heterogeneity with mainly worsening course was observed in the previous reports of thirty-one individuals with *FBXL4* mutations. Progressive CNS involvement seems characteristic for MTDPS13; the oldest reported individual is 13-year old with severe neurological sequels post stroke-like episode.
The family presented here showed predominant gastroenterological and immunological involvement. The variability of CNS involvement between the two affected siblings but especially the favorable neurological outcome of the oldest sibling are expanding the clinical spectrum of this condition.
Keywords: Mitochondrial disorders, MtDNA depletion, gastropathy, neutropenia, *FBXL4*

P105 Second family with Mabry Syndrome caused by *PIGL* mutation
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Objectives: To describe the second family with Mabry syndrome (*H*yper*p*hosphatasia *mental retardation syndrome-HPRMS) caused by PIGL mutation.*
Design and Methods: Clinical evaluation and molecular testing of two siblings presented to our institution with distinctive facial features, developmental delay, mental retardation, seizure disorder, skeletal deformities, and high alkaline phosphatase.
Results: Molecular testing for the index case showed two heterozygous mutations in PIGL gene (C.60G>A; p.TRP20*, and c.262C>T; p.ARG88Cys). Segregation analysis confirmed compound heterozygous inheritance of the two alleles. Same changes found in the other affected sibling.
To date, six mutations in PIGL gene have been identified in seven patients presenting with CHIME syndrome (*c*oloboma, *h*eart defect, early-onset *i*chthyosiform dermatosis, *m*ental retardation and *e*ar anomalies /hearing loss alternate with *e*pilepsy) and only one patient with Mabry phenotype (Am J Med Genet A.2015Apr:167A(4):777-85). In our patients, some of the clinical features overlap between CHIME and Mabry syndrome especially the CNS involvement; however, they do not have coloboma, heart defect or hearing impairment. The distinctive skeletal phenotype of short terminal phalanges and the high alkaline phosphatase diverged our diagnosis to Mabry syndrome.
Conclusions: Our clinical, biochemical and molecular findings support the previous report of Mabry syndrome caused by *PIGL* mutation, which is another Phosphatidylinositol Glycan (PIG) anchor biosynthesis class that should be considered in the differential diagnosis of the known PIG classes *(PIGV, PIGO, and PIGW)* and the Post GPI Attachment to Proteins genes *(PGAP2, PGAP3)* that are currently linked to Mabry syndrome.
Keywords: *H*yper*p*hosphatasia *m*ental *r*etardation *s*yndrome (HPMRS), Mabry syndrome, *PIGL* gene, CHIME syndrome, autosomal recessive intellectual disability.

P106 Discrepant genotype-phenotype correlation in two siblings with hypophosphatasia
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Background: Hypophosphatasia (HPP) is a rare genetic disorder causing defective bone mineralization, due to a deficit of tissue-nonspecific alkaline phosphatase (TNSALP), encoded by the *ALPL* gene. The clinical severity and age of onset vary greatly and are thought to reflect residual enzyme activity. There is, however, a more limited intra-familial variation, and affected siblings sharing the same genotype tend to be similarly affected.
Objectives: We report on two siblings that are followed in our clinic. Both are compound heterozygotes for *ALPL* mutations: c.571G>A in exon 6 and c.1553_1568del16 in exon 12. However, they are both differentially affected, with the oldest having findings typical of childhood type HPP and the youngest having almost exclusively dental findings, more in keeping with odontohypophosphatasia.
Design/Method: We compare the phenotype of the two siblings by reviewing the clinical findings, imaging and laboratory results.
Results: Sibling 1, the oldest, presented between one and two years of age with loss of four primary teeth, an ankle fracture and x-ray anomalies including decreased bone density and rachitic changes. His alkaline phosphatase level was 20 U/L. Sibling 2 was diagnosed prenatally through molecular testing, and presented clinically after one year of age with tooth decay and hypoplastic, abnormally shaped teeth. Her ALP level was 23 U/L. She has not had any skeletal complications, including fractures.
Conclusions: Our report adds to the available descriptions of genotype-phenotype correlations in HPP and increases awareness to the phenomenon of intra-familial phenotypic discrepancy.
Keywords: Hypophosphatasia, alkaline phosphatase, bone mineralization.
Funding: The presenter of this abstract was supported by an educational grant from Alexion Pharmaceuticals Inc.

P107 Harderoporphyria following bone marrow transplantation; a case report of two siblings
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Design and Methods: Here, we present the long-term follow-up for two siblings (now 12 and 17 years of age) with harderoporphyria who received matched unrelated bone marrow transplantation in infancy because of a misdiagnosis of osteopetrosis.
Results: Harderoporphyria is a rare form of porphyria caused by a specific homozygous mutation in the coproporphyrinogen oxidase gene (p.404K>E). Patients with harderoporphyria are severely affected as infants with jaundice, hemolytic anemia and blistering skin lesions, especially in response to phototherapy for hyperbilirubinemia. Symptoms in later life tend to be fairly mild, with cutaneous sensitivity being the major manifestation. Both siblings have high (>90%) donor chimerism post-transplant. The older sibling continues to excrete coproporphyrin III in urine at levels consistent with those in reported patients with harderoporphyria. However both patient lack cutaneous photosensitivity and the hemolytic anemia seen typically seen in older patients with the condition.
Conclusions: To our knowledge these siblings are the only patients with harderoporphyria who have received bone marrow transplant. Their clinical course suggests that the procedure is effectively curative although the associated risks of transplant are unlikely to justify its use in harderoporphyria management. This case adds to our understanding of the organ-specific effects of porphyrias.

P108 Acid Lipase Deficiency from Diagnosis to Therapy in Canada
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Background: Lysosomal Acid Lipase (LAL-D) deficiency is an ultra-rare lysosomal storage disorder. Clinical features in the late-onset form include dyslipidemia (elevated LDL, low HDL), elevated liver enzymes, hepatomegaly, and splenomegaly. This can progress to liver fibrosis and cirrhosis. LAL-D is caused by deficient activity of the LAL enzyme, resulting in the accumulation of cholesteryl esters and triglycerides throughout the body, predominately in the liver, spleen, gastrointestinal tract, and blood vessel walls. Supportive management with lipid-modifying agents, hematopoietic stem cell and liver transplant has been without major success.
Methods and Results: Over the last 20 years we have had three patients with a confirmed diagnosis of LAL-D. Two adult patients, currently 31 and 40 years old, were diagnosed at 11y and 14 y with LAL activities at about 7% of control mean using fibroblasts and peripheral blood leukocytes after presenting with hepatosplenomegaly (A Nine year old girl of French and Welsh background presented with hepatomegaly, elevations in liver enzymes and dyslipidemia. LAL

enzyme showed low levels of 13 pmol/hour (normal 80-230) in dried blood spots. She has c.684delT and c.894G>A pathogenic mutations.
Discussion: The third patient has received Sebelipase Alfa Kanuma®, intravenous therapy every two weeks at 1 mg/kg. The therapy was started after significant advocacy from the family as the drug is not yet approved for coverage in Canada. She has tolerated the infusions well for the last three months with no side effects. The liver enzymes and lipid profile have nearly normalized. Preliminary results appear to be encouraging.

P109 National PKU Alliance Patient Registry

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Objectives: The implementation of an outcomes oriented patient registry for phenylketonuria (PKU) expands our knowledge basis on the variability of the clinical phenotype, identifies unmet needs and guides the scientific community in the development of novel therapies.
Design and Methods: The NPKUA Patient Centered Outcome Registry, launched in January 2017 is a global registry for patients with PKU. The registry collects information from families/participants who are affected by PKU and are interested in participating in future research. The registry utilizes a web- based interface (https://pku.iamrare.org) to maximize accessibility to participating families and clinics at a global scale. Registry participants will automatically be enrolled in the Global Rare Disease Registry (GRDR), and their de-identified information aggregated with information from other rare diseases. Third parties may seek access to data in the PKU Patient Registry. Third parties may include, researchers or companies conducting retrospective studies or conducting research and/or clinical trials on new therapies and will only be granted access upon review and approval of the Registry Advisory Board.
Utilizing a survey format, the registry collects data on long-term metabolic control and management, co-morbidities, general health and life style, social-economic factors and genotypes. Access to phenylhydroxylase gene sequencing is facilitated through collaboration with Baby Genes (www.babygenes.net).
Results and Conclusions: Registry enrollment within 4 weeks of launch exceeded 200 with participants from the US and Canada. Marketing efforts utilizing social media and partners in industry and the clinical setting proved to be successful with a favorable response from the PKU community.

P110 CMPK2, a mitochondrial enzyme in the nucleotide salvage pathway, might be related to a MNGIE-like phenotype – Case Report

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Objectives: Mitochondrial DNA depletion syndromes (MDS) are caused by genetic defects involving different pathways (Neuromuscul Disord 2010;20(7):429-37). Mitochondrial neurogastrointestinal encephalopathy (MNGIE, MIM 603041) is a MDS caused mainly by mutations in TYMP (thymidine phosphorylase, MIM 131222), an enzyme involved in the nucleotide salvage pathway (NSP). Here, we describe a new case of MNGIE-like phenotype with mutations in another enzyme of the NSP, CMPK2 (cytidine monophosphate kinase 2, MIM 611787, NM_1256478), never reported before.
Design and Methods: An 11 years old boy was referred with severe myopathy, failure to thrive, abdominal pain, gastrointestinal dysmotility, global developmental delay, gait instability, neuropathic pain, neurogenic bladder and dysautonomic signs, progressing since age 5. Physical exam revealed cachexia, muscle atrophy, proximal weakness, and signs suggestive of a peripheral neuropathy. Thymidine testing was negative for TYMP deficiency. Mitochondrial complexes study by Blue Native-PAGE on muscle revealed a generalized diminution of all 5 complexes.
Results: Two heterozygous CMPK2 mutations were found by WES, c.59G>C (p.Arg20Pro) and c.1027C>T (p.Leu343Phe). Both mutations were confirmed by Sanger sequencing. Parental analyses confirmed that mutations were in trans. The c.59G>C and c.1027C>T have a prevalence in ExAC of $3.4X10^{-4}$ and $9.3X10^{-5}$, respectively. CMPK2 is a UMP-CMP kinase located in the mitochondria and involved in the NSP, phosphorylating dUMP, dCMP and CMP (J Biol Chem 2008;283(3):1563-71).
Conclusion: Homozygous or compound heterozygous mutations in CMPK2, a mitochondrial enzyme involved in the NSP, might be related to a MNGIE-like phenotype. More patients and functional studies are needed to understand the pathophysiology of the disease.
Keywords: Mitochondrial Disease, MNGIE, Nucleotide Salvage Pathway, CMPK2

P111 Health care for mitochondrial disorders in Canada: A survey of physicians

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Objectives: Our three objectives are to: (a) describe care for patients with mitochondrial diseases in Canada, with respect to the providers involved and services available; (b) investigate the basis for variation in care, with respect to diagnostic tests, monitoring and treatment; and (c) describe Canadian clinicians' views on research priorities for patients with mitochondrial diseases.
Design and Methods: We used multiple sources of ascertainment to identify Canadian physicians who may provide diagnostic care and/or treatment for mitochondrial disorders. Our initial sample was derived through the professional networks of our clinical advisory group and through publicly available membership lists of relevant professional

organizations. Sampled physicians were contacted by mail up to five times and invited to complete a questionnaire by mail or web. As part of the questionnaire, participants identified other potentially eligible physicians who were then invited by the research team to participate (snowball sampling). We developed a questionnaire covering the following topics: experience in providing care for patients with mitochondrial disorders, diagnostic and management practices, challenges in accessing diagnostic tests or treatments, research priorities, and personal and practice characteristics.
Results: Our initial sample included 90 physicians and this has been expanded to 107 physicians through snowball sampling. Data collection is underway with 38 responses received so far.
Conclusions: The findings of this study will be used to understand the provision of health care for patients with mitochondrial disorders in Canada in order to establish priorities for current and future interventions and to catalyze Canadian research in this field.
Keywords: Mitochondrial disease, diagnosis, treatment, practice patterns, survey
Funding Acknowledgement: This study was supported by MitoCanada and in-kind support from the Canadian Inherited Metabolic Diseases Research Network (CIHR – grant TR3-119195).

P112 Sapropterin (Kuvan) responsiveness and usage in Phenylketonuria
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Objectives: To examine the determination of responsiveness in a Sapropterin trial. To examine pre and post outcomes measures in responsive patients. To determine the effects of dose reduction in responsive patients.
Design and Methods: This is a retrospective review of clinical data. We used a 4 week trial of Sapropterin to determine responsiveness (dose 20mg/kg/day; days -14,-7, 0, 3, 7, 14, 21 and 28). Responsiveness was determined by a 30% drop in plasma or blood spot Phe levels. We reviewed the Phe and Tyr levels during the trial. In responsive patients, we examined Phe and Tyr levels as well as natural protein tolerance in patients for a period of +/-12 months. Finally we looked at the effects of reducing Sapropterin dose in responsive patients.
Results: Several factors complicating the interpretation of responsiveness were identified, including determining initial Phe tolerance, achieving adequately high levels of initial Phe, the presence of early false and late true responses, as well as maintaining steady state conditions during the trial (eg intermittent illness, improved dietary adherence). The trial was extended in a number of patients. While long term improvements were seen in some responsive patients, in others plasma Phe levels increased while on medication. Several patients were maintained successfully on lower doses.
Conclusions: The determination of Sapropterin responsiveness is complex. Long term pre and post Phe levels must be followed to ensure compliance and effectiveness of the medication. Responsive patients can be maintained on lower doses (eg 10 mg/kg/day) without changes in Phe levels and with considerable cost savings.

P113 Is misoprostol porphyrogenic? A Case Report
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Objectives: The acute porphyrias are a group of inherited disorders characterized by acute attacks that may be precipitated by a variety of conditions and medications. We report here the first case in the literature of an acute attack associated with the use of misoprostol, an agent used to expel products of conception.
Design and Methods: Patient A is 32 y.o female G2P2A1 who belongs to a family with a mutation associated acute intermittent porphyria (AIP) (*HMBS* c.219-220delGA). The observations were taken from her chart. PBG and 5-ALA are determined quantitatively using Ehrlich's reagent (Bio-Rad).
Results: Patient A suffered a foetal demise at 11 weeks of pregnancy and was treated with misoprostol (400 µg PV x 4). After repeating this treatment, she developed acute abdominal pain. She was admitted to the ER and was treated successfully with heme arginate with resolution of her symptoms. Immediately prior to treatment, her PBG was 24.9 micromol/millimol Cr and 5-ALA 22.0 micromol/millimol Cr. Two days post treatment these declined to 4.6 and 4.9, respectively.
Conclusions: While many compounds have been reported to be porphyrogenic, the rareness of this disease makes it difficult to establish a clear association. Misoprostol is not listed as porphyrogenic in at least one database (www.porphyriafoundation.com/drug_database/drug-list.php?cl=&t=&g=misoprostol&b=&co=). Thus, we are dependent on the accumulation of case reports to establish a link between such disorders and the use of any compound.
Keywords: acute intermittent porphyria, misoprostol

P114 Riboflavin transport deficiency mimicking mitochondrial encephalomyopathy caused by complex II deficiency
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Background: Riboflavin transport deficiency (RTD), Brown-Vialetto-Van Laere Syndrome, is characterized by muscle weakness, ataxia, progressive ponto-bulbar palsy, amyotrophy, and sensorineural hearing loss and inherited autosomal recessively. It is caused by likely pathogenic variants in three genes, SLC52A1, A2, A3. Pharmacologic doses of oral riboflavin halt disease progression and may reverse symptoms. We report two new patients with variable phenotype.
Patients and Results: Patient 1 is an 8 year old male, who presented with progressive gross motor delay, axial and appendicular hypotonia, ataxia, and mild dysarthria at 2 years of age. He was diagnosed with bilateral sensorineural hearing loss. Due to mild to moderate lactate elevations, he underwent a muscle biopsy. Respiratory chain enzyme activity measurement showed marked complex II deficiency (21.93 nmol/min/mg protein, reference range 107.66-230.11, 13% of mean). Muscle histochemistry showed ragged red fibers. Nerve conduction studies demonstrated absent sensory nerve responses. Whole-exome sequencing revealed a homozygous likely pathogenic variant in SLC52A2 (c.917G>A; p.G306E). Riboflavin at 70mg/kg/day was tolerated well.
Patient 2 is a 9 month old boy, who presented gross motor delay at the age of 3 months, which progressed to acute respiratory insufficiency requiring ventilator support following an upper respiratory tract infection. Muscle respiratory chain enzyme activity measurement showed combined complex II + III deficiency (0.63 umol/min/g protein, reference range 0.67-3.03, 30% of mean). Rapid whole-exome sequencing identified a homozygous likely pathogenic variant in SCL52A3 (c. 1223G>A; p.G408D). He tolerated 70mg/kg/day riboflavin therapy.
Conclusion: We report two new patients with riboflavin transporter deficiency, caused by mutations in two different riboflavin transporter genes. Both patients presented with respiratory chain complex II deficiency. This treatable neurometabolic disorder and can mimic mitochondrial encephalomyopathy. In patients with complex II deficiency, riboflavin transporter deficiency should be included in the differential diagnosis to allow early treatment and improve neurodevelopmental outcome.

P115 Variation in diagnostic care and disease classification for PAH deficiency: Initial findings from the Canadian Inherited Metabolic Diseases Research Network (CIMDRN)

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Objectives: To describe patterns of diagnostic care for a cohort of Canadian children diagnosed with phenylalanine hydroxylase (PAH) deficiency, and investigate methods for assigning disease classification according to genotype, biopterin response, peak blood phenylalanine (Phe) concentrations, and prescribed dietary Phe.

Design and Methods: Children with PAH deficiency, born between 2006 and 2015, and receiving care in one of 13 participating metabolic clinics were eligible to participate in the Canadian Inherited Metabolic Diseases Research Network (CIMDRN). From patient charts, we collected baseline observational data on demographic and clinical characteristics, disease ascertainment, and diagnostic care; and longitudinal data on monitoring tests, interventions received, and clinical outcomes.

Results: Analyses are underway. To date (February 2017), 183 children with PAH deficiency have been enrolled in CIMDRN, of whom, 90 (49%) have complete baseline data. Newborn screening was the ascertainment method for most participants (97%). Median age at diagnosis was 10 days (range 2-230). Median initial dietary Phe prescription for patients with phenylketonuria (PKU, peak diagnostic blood Phe concentration >=600umol/L) was 200 mg Phe/day (range 0-338) compared to a median initial dietary Phe prescription of 373 mg Phe/day (range 65-2500) for those with non-PKU hyperphenylalanemia (peak diagnostic blood Phe concentration 120-600umol/L). Biopterin response and genotype also varied across these two disease classifications. Analyses are ongoing to determine if alternative measures (e.g., peak blood Phe during follow-up) can be used to assign disease classification.

Conclusions: Practice variation was identified for diagnostic care. Next steps include a comprehensive analysis of longitudinal clinical data for PAH deficiency.

P116 The role of coping strategies in the association between caregiving complexity and quality of life among parents of children with inherited metabolic diseases

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Objective: It has been hypothesized that positive approaches to coping may be associated with better quality of life (QoL) among parents of children with chronic illness. In our previous qualitative study, parents of children with inherited metabolic diseases (IMD) reported a range of proactive coping strategies that they perceived as important to managing their child's care. The aim of the present study is to further investigate the association between coping and QoL among parents of children with IMD in a large sample of families from across Canada.

Design and Methods: Parents of children with an IMD enrolled in the Canadian Inherited Metabolic Diseases Research Network (CIMDRN) cohort (n>600) at one of 13 participating centres are eligible to participate in this cross-sectional survey. Parents are invited to complete a mailed questionnaire that includes validated measures of parent QoL (SF-12), parental coping strategies (WAYS of coping scale), caregiving complexity (from the Child Health Questionnaire) as well as socio-demographic characteristics. Multiple linear regression analyses will be conducted to investigate associations among these measures and to determine whether coping is an effect modifier of the association between caregiving complexity and QoL in this population.

Results: Data collection is underway; preliminary results will be presented.

Conclusions: This study will help us to understand the role of coping as a potential contributor to QoL among parents of children with IMD. The findings will help to inform the development of interventions that aim to promote improved well-being for children with IMD and their families.

Keywords: Quality of life, coping, parents, inherited metabolic diseases

P117 Moving Towards Clinical Gene Therapy of GM2 Gangliosidosis: An Update

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GM2 gangliosidosis are neurodegenerative disorders caused by a deficiency of either Hexosaminidase A enzyme (HexA) or the GM2 Activator protein (GM2A). HexA consists of α- and β- subunits, which when mutated cause Tay-Sachs disease (TSD) and Sandhoff disease (SD), respectively. GM2A deficiency causes TSD – AB variant (TSD-AB). In ongoing studies, we assessed the effect of Adeno-associated virus 9 (AAV9) viral vectors incorporating the transgenes -*HEXM* (encoding a hybrid subunit with properties of α- and β- subunits), *HEXA/HEXB* or *GM2A* in disease mouse models via intravenous delivery in varying doses and ages. We monitored for survival/locomotion and biochemical outcomes in the SD and TSD-AB mice. The AAV9-*HEXM* treated SD mice survived significantly longer, an average of 58.8 weeks of age, with the oldest mouse surviving to 89 weeks, as compared to 16 weeks humane survival for untreated SD mice. Since TSD-AB mice have a normal life span, the significant endpoints are GM2 ganglioside reduction in the brain and behavioural testing. Biochemical data shows a decrease in GM2 storage in gene therapy treated groups of both mice as compared to untreated mice. In addition, the behavioural data showed that *HEXM* treated mice perform better than untreated controls. Results from this study demonstrate corrective abilities of our AAV based vectors when administered in respective mouse models. Histological and molecular analyses are ongoing. These results provide a crucial step forward for human translation and we are currently working on clinical trial applications for Health Canada for all forms of GM2 gangliosidosis.

P118 The application of a magnetic resonance imaging algorithm in the clinical diagnosis of white matter abnormalities

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Background: White matter abnormalities (WMA) reported on cranial magnetic resonance imaging (MRI) often pose a diagnostic challenge when trying to establish an etiologic diagnosis. During childhood and adult years, genetic and metabolic disorders in addition to acquired conditions are included in differential diagnoses. To help clinicians and radiologists, a structured algorithmic has been recommended to aid in establishing working diagnoses that will facilitate appropriate biochemical and genetic investigations.
Objective: This retrospective pilot study investigated the validity and diagnostic utility of such an algorithm for patients seen in our clinics.
Methods: The MRI algorithm was applied to thirty-one patients selected at random from patients attending the neurogenetic and neurometabolic clinic at a tertiary care hospital. These patients varied in age from 5 months to 79 years old, and presented confirmed white matter signal abnormalities (WMSAs) on cranial MRIs. Twenty-one patients had a confirmed biochemical genetic diagnosis and 10 patients had confirmed non-specific WMA diagnoses (etiology unknown). Two radiologists, blinded to confirmed diagnoses, used patient MRI scans and clinical abstractions to classify possible WMA diagnoses through utilizing the algorithm.
Results: The MRI algorithm displayed a sensitivity of 100%, a specificity of 30.0% and a positive predicted value of 74.5%. Cohen's kappa statistic for inter-radiologist agreement was 0.733, suggesting "good" agreement between radiologists.
Conclusions: Although a high diagnostic utility was not observed, results suggest that this MRI algorithm has promise as a clinical tool for clinicians and radiologists. This study has identified various benefits and limitations of this approach for future directions.
Keywords: white matter abnormalities, myelination, magnetic resonance imaging, diagnostic utility, diagnostic neuroradiology

P119 Carnitine palmitoyltransferase 2 (CPT2) deficiency: gray matter heterotopias in a patient with infantile clinical onset and normal development

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Objective: To study the occurrence of cerebral malformations in infantile CPT2 deficiency. Neuronal migration defects are well-described in lethal neonatal CPT2 deficiency. We report a male with CPT2 deficiency who presented clinically at 5 months of age. He also has an unrelated condition, X-linked nephrogenic diabetes insipidus. He has had normal development, but cerebral MRI after an afebrile convulsion at 17 years of age revealed extensive left temporo-parieto-occipital polymicrogyria with white matter heterotopias and schizencephaly.
Design and Methods: We searched Pubmed, Google scholar and the bibliographies of the articles found by these searches, for infantile CPT2 deficiency and for cerebral malformation in infantile or later-onset patients. Exclusion criteria included insufficient information about age of clinical onset or phenotype and lack of confirmed CPT2 deficiency by enzymatic assay or genetic testing. Each phenotypic description was analyzed for the presence of cerebral malformations, and for whether investigations were performed for brain malformations (e.g., imaging or autopsy).
Results: 23 cases were found, of which 17 (74%) met the inclusion criteria. Brain malformations were not previously reported in infantile CPT2 deficiency discovered by the literature search, but only 2/17 (11.8%) of these published cases mentioned brain imaging or pathology data.
Conclusions: To our knowledge, this is the first report of a neuronal migration defect in a CPT2-deficient patient with post-neonatal clinical onset. The frequency of brain malformations may be underestimated in this population because cerebral imaging is rarely performed in CPT2 deficiency.

P120 Describing MCADD management using Canadian pediatric data: preliminary findings on genotype and phenotype

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Objectives: Previous research has identified variation in care for children with medium-chain acyl CoA dehydrogenase deficiency (MCADD), particularly in the context of asymptomatic identification via newborn screening. Our objective is to describe care received by Canadian children with MCADD, including variations in care according to genotype as a proxy indicator of disease severity.

Design and Methods: We are analyzing clinical data from the Canadian Inherited Metabolic Disease Research Network (CIMDRN) cohort study. Among children with MCADD enrolled in CIMDRN at one of 13 participating centres and born between 2006 and 2015, we are extracting information on means of ascertainment, genotype, biochemical phenotype (octanoylcarnitine [C8] levels), patient age and sex, and care received (frequency of clinic and emergency department visits, prescribed duration of fasting, use of carnitine).

Results: Analyses are underway. Sixty-five children diagnosed with MCADD are enrolled in CIMDRN to date, of whom 57 have complete baseline data. 56 (98 %) were ascertained via newborn screening. The median age at diagnosis was 11 days. Molecular genetic testing results for the ACADM gene and diagnostic C8 levels were available for 34 participants. Diagnostic C8 levels differed by genotype: 13 were homozygous for the common c.985A>G mutation (median C8: 3.10 umol/L), 14 were compound heterozygous for the common c.985A>G mutation (median C8: 1.86 umol/L), and 7 were other genotypes (median C8: 0.78 umol/L).

Conclusions: Newborn screening led to early diagnosis of MCADD while uncovering a broader clinical spectrum. This study represents a first step toward informing appropriate care for affected children.

P121 Systematic and scoping reviews to identify guidelines and actual practice for the diagnosis and management of MCADD and VLCADD

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Objectives: Limited evidence supports the effectiveness of interventions for the diagnosis and management of medium-chain acyl CoA dehydrogenase deficiency (MCADD) and very-long-chain acyl CoA dehydrogenase deficiency (VLCADD), particularly in asymptomatic infants identified by newborn screening. We conducted a systematic review of guidelines and a scoping review describing actual practice for the diagnosis and management of these conditions.

Design and Methods: We developed electronic search strategies for both reviews in MEDLINE, Embase and grey literature. Two independent reviewers assessed eligibility of citations in two stages of screening. Eligible guidelines were formal recommendations developed using expert consensus, empirical evidence, or a combination of methods. Eligible reports of actual practice were primary studies with ≥5 participants, published since 2000 in peer-reviewed literature. Information on publication characteristics, methods and key results are being abstracted and synthesized narratively. Guidelines will be appraised using the AGREEII tool.

Results: The systematic review search strategy identified 1226 citations, 15 of which met final inclusion criteria. Ten guidelines were expert opinions/reviews, one was based on a consensus panel, one was founded on empirical evidence and three used a combination of methods. Guidelines described diagnostic and confirmatory tests and their timelines, emergency and long-term care, fasting, dietary and medical recommendations and care during intercurrent events. From an initial retrieval of 2072 records, 30 citations met inclusion criteria for screening in the scoping review.

Conclusions: Preliminary review of guidelines for the management of MCADD and VLCADD has identified limited high-quality guidance for physicians involved in managing these metabolic disorders.

P122 Mild hypersuccinylacetonemia in Quebec: genetic diversity and therapeutic implications

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Objective: To determine the cause and course of mild hypersuccinylacetonemia (MHSA) in 8 SA-positive newborns referred to Québec NTBC Study (QNS) Group physicians. Hepatorenal tyrosinemia (HT1), due to severe FAH deficiency, is reliably detected by screening for succinylacetone (SA). We hypothesized that defects of terminal phenylalanine & tyrosine (phe/tyr) degradation may cause MHSA.

Results: Six MHSA patients (Yang, 2016 PMID 27876694) had mutations in *GSTZ1*, encoding MAAI, the second-last enzyme of phe/tyr degradation: 4 were c.449C>T (p.A150V) homozygotes; one, a compound of c.259C>T(p.R87X) & c.68-12G>A; one, a c.295G>A(p.V99M) heterozygote with no identified second mutation. Bacterial expression of *GSTZ1* cDNAs showed 56% residual activity for c.449C>T and 27% for c.295G>A. Two other MHSA patients had the known "pseudodeficient" p.R341W FAH allele (7-13% activity, Rootwelt 1994, PMID 7977370) and a splice mutation. In contrast with HT1, all 8 MHSA newborns had normal coagulation testing. Liver function & imaging are normal without treatment in all MHSA individuals studied.

Discussion: Precise diagnosis of elevated SA is critical: MHSA is not treated but HT1 requires urgent treatment. On NTBC treatment, MHSA would be indistinguishable from HT1. Current data do not support treatment for MHSA with normal liver function (normal coagulation & AFP). To date, elevated INR has accurately distinguished HT1 from MHSA. Followup of liver function & imaging are planned for MAAI patients. The SA levels of compounds for pseudodeficient/severe FAH mutations may help in defining the goals for acceptable HT1 treatment.

Conclusion: Mild FAH deficiency and at least some MAAI mutations produce MHSA.

Keywords: tyrosinemia, succinylacetone, NTBC, FAH, MAAI.

P123 Case Study: A practical application of the simplified PKU diet

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The objective of this case study is to show the transition a family made from a strictly controlled traditionally monitored PKU diet to the more simplified method of management. In the traditional method, phenylalanine (PHE) intake is counted in milligrams (mg) of PHE, and ALL foods except those completely devoid of PHE are counted in the daily intake. In the simplified method, fruits, most vegetables and low protein foods do not count towards the daily PHE intake, and intake is measured in grams of protein instead of milligrams of PHE. In this case, the family and dietitian chose to make the transition very slowly, by eliminating groups of foods from the daily count in stages, reducing the target PHE intake accordingly, and closely monitoring blood-PHE levels to ensure stability before moving on to the next phase. The results clearly indicate that both methods are effective at controlling blood-PHE levels, and the family reports a significant lessening of the burden of care associated with the disorder with each stage of the process. This study, ultimately, could be a good resource for dietitians who want to introduce this method to families, as a way to assure families that it is safe, effective and results in positive changes for the daily management of PKU without compromising blood-PHE levels.

P124 The Range of Intakes of Phenylalanine and Tyrosine among Quebec Tyrosinemia Type 1 Patients in a Single Center

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Objective: To ascertain the phenylalanine (Phe) and tyrosine (Tyr) tolerance of medically-treated patients with hereditary tyrosinemia type 1 (HT-1), an autosomal recessive inborn error of Phe+Tyr degradation. Treatment of HT-1 is a combination of nitisinone (NTBC) plus a low Phe+Tyr diet. NTBC blocks an early step of Phe and Tyr degradation. Consequently, plasma Phe and Tyr levels respond to diet with more sensitivity than in non-NTBC-treated patients.
Methods: Retrospective data (dietary journals, biochemical/clinical data) of 31 NTBC-treated patients (aged 16 months to 28 years) from the CHU Sainte-Justine branch of the Quebec NTBC Study. We looked at growth, Phe+Tyr intake, plasma Phe & Tyr levels, and Phe supplementation. All patients received dietary Phe+Tyr restriction, calculated by a Phe+Tyr exchange system (1 exchange= 25 mg Phe+Tyr).
Results: In ~60% of patients, plasma tyrosine levels are in the target range (200-400 µmol/L). Mean total daily Phe+Tyr intake ranged from 315 to 1100 mg/day. Phenylalanine supplementation varied from zero (16 patients, 52%) to 240 mg/day. Some variability of Phe and Tyr levels may be due to infections or other stress. However, most values were obtained on well days. Individual patients tended towards stability of Phe+Tyr levels and tolerance.
Conclusion: Phe+Tyr intakes differ greatly among HT-1 patients, even at a single center. Potential determinants are under analysis. We hope to extend this study to other Québec NTBC Study centers. Close follow-up, attention to growth and individualization of dietary intake, are important for dietary control in HT-1.

P125 MMA-PA patients

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A high ratio of natural protein to artificial amino acids is associated with good metabolic control and low risk of decompensation in methylmalonic acidemia (MMACoA mutase deficiency) or propionic acidemia (PA) patients.
Background: MMA and PA are severe organic acidemias, characterized by acute metabolic decompensation, poor growth and multi-organ symptomatology.
Method: Retrospective study clinical, biochemical and dietary findings of 8 patients (2 MMACoA mutase deficiency, 6 PA) treated and followed at CHU Sainte-Justine over 16 years. In each family, the proband became symptomatic and was diagnosed before one year of age.
Results: All (n=8) patients received an average ratio of 85% of natural protein to artificial amino acids. Weight and height were close to predictions from midparental values. With the exception of one PA patient with cardiomyopathy and chronic hyperammonemia, none of the 7 other patients had chronic or acute elevation of ammonia. During the 63 patient-years of follow-up, the number of hospitalisations for acute decompensation totaled 8 (0.13/patient/year).
Conclusion: Our data suggest better metabolic control in PA and MMACoA mutase deficiency patients with a higher natural protein to artificial amino acids ratio. Except one patient, all others (7/8) experienced only few metabolic decompensations.

P126 Application of next-generation sequencing as a diagnostic tool for mitochondrial disease in Calgary

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Objectives: To test the yield of next generation sequencing (NGS) on cases already investigated for a mitochondrial disease using conventional methods.
Design/Methods: Our conventional protocol for investigating mitochondrial disease involves a brain MRI, blood and urine biochemistry, muscle histology, electron microscopy, biochemistry, and muscle-extracted mtDNA testing. This study was a prospective trial recruiting patients who had been investigated for mitochondrial disease using these conventional methods to evaluate the utility of re-testing using a custom panel of at least 300 genes nuclear genes (nDNA) using NGS.
Results/Conclusions: We previously reported an analysis on 292 patients investigated for mitochondrial disease (children and adults) and found 102 were diagnosed with a mitochondrial disease (MD), 71 were eventually diagnosed with another disease (OD) and 118 had no specific diagnosis (ND). In the MD group, 11 patients were recruited of which a confirmed nDNA pathogenic mutation was found in 3 cases (*TRMU, FBXL4, TFSM*), suspicious candidates in 3 cases (*NDUFS3, ATP10A, GFM1*), 1 case was found to have a suspected mutation that does not cause mitochondrial disease (*CDKL5*) and there were 2 cases with a known mtDNA deletion where no nuclear gene mutations were found for mitochondrial disease. In the patients from the ND group, 4 were recruited and none were found to have nDNA mutations. Overall, NGS provided a more specific diagnosis but yielded a possible alternative diagnosis on only 1/15 cases investigated through conventional methods and did not change the therapy in any case.

P127 Understanding the Molecular Mechanisms in Pyruvate Dehydrogenase Deficiency Outcomes and Treatment

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Background/Objectives: Pyruvate Dehydrogenase Complex Deficiency (PDCD) is a clinically heterogeneous disorder, usually presenting with lactic acidemia and neurological manifestations that may be progressive or intermittent. Outcomes in PDCD vary from infantile death to severe intellectual disability, the basis of which is largely undetermined. Treatment with ketogenic diet or thiamine also has variable effectiveness. The objective of this study was to report five case of PDH deficiency and to examine for a genotype-phenotype correlation to outcome and responsiveness to treatment.
Methods: A retrospective chart analysis was performed on five cases of PDCD (3 female and 2 male).
Results: The average age of symptom onset was 6 weeks (range1-3 months) in females and 18 months (range 9-24 months) in males. The average age of diagnosis is 5 months and 5 years in females and males respectively. 20% (1/5) have died and 80% (4/5) have cognitive delay.

20% (1/5) was responsive to thiamine treatment. 80% (4/5) have undergone molecular testing and mutations on *PDHA1* have been identified in 75% (3/4).
Conclusion: The case reports highlight the phenotypic heterogeneity of PDH deficiency. One case was very successfully responsive to thiamine. This case had a mild mutation (in-frame insertion) and presented with a much milder phenotype than usually observed in males suggesting there may be a genotype-phenotype correlation. We intend to perform E1 alpha subunit phosphorylation/dephosphorylation studies and structural modelling to investigate if this explains the wide variation in phenotypes and responsiveness to treatment.
Keywords: Pyruvate Dehydrogenase Deficiency, treatment, thiamine

P128 Infantile Neuroaxonal Dystrophy – Two Early Diagnosed Cases Presenting With Developmental Regression and Cerebellar Atrophy
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Background/Objectives: Infantile neuroaxonal dystrophy (INAD) is a *PLA2G6*-associated neurodegenerative condition characterized by infantile onset of rapid motor and cognitive regression, hypotonia evolving into spasticity and cerebellar atrophy. Due to the overlapping phenotypes and heterogeneity of clinical findings, diagnosis is often difficult and traditionally patients endured long diagnostic odysseys. The objective of this study is to report two cases of early diagnoses of INAD by whole-exome-sequencing (WES).
Methods: A retrospective chart analysis was performed.
Results/Case Reports: Patient 1 is a two year one month old boy, born to non-consanguineous Chinese parents, with regression of motor skills and dysphagia from 16 months. Patient 2 is two year three month old boy, born to consanguineous Pakistani parents, with global developmental delay followed by regression apparent by 22 months. Both had profound head lag, truncal hypotonia, axial hypertonia, and brisk deep tendon reflexes. Nystagmus and auditory sensory neuropathy were also present in Patient 2. MRI demonstrated mild cerebellar atrophy with normal white matter and myelination in both cases, with additional mild hyperintensity of the caudate and lentiform nuclei in patient 2. Pathogenic variants in *PLAG26*, which affected splicing causing protein truncation, were identified in both patients by rapid WES (results within two weeks).
Conclusion: Such early diagnosed cases add to the natural history and the genotype-phenotype correlation of INAD. INAD is highlighted as a possible diagnosis in patients presenting with developmental regression, auditory neuropathy spectrum disorder and cerebellar atrophy. The benefit of WES for rapid diagnosis in clinical practice is also evident.
Keywords: cerebellar atrophy, developmental regression, auditory neuropathy, *PLA2G6*.

P129 Pharmacologic chaperone responsiveness in Canadian patients with Fabry disease
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Fabry disease (FD) is an X-linked lysosomal storage disease due to deficiency of the enzyme α-galactosidase. This results in premature death from renal failure, hypertrophic cardiomyopathy and strokes. Treatment with intravenous enzyme replacement therapy (ERT) is expensive and not curative. Pharmacologic chaperone therapy (PCT) with Migalastat, an oral iminosugar, increases residual enzyme activity by stabilizing the molecule and delivering more enzyme to the lysosome.
Objective: We report the prevalence of chaperone responsiveness in Canadian Fabry disease patients.
Design and Methods: The Canadian Fabry Disease Initiative (CFDI) is a registry of 466 FD patients followed for up to 10 years. All known GLA mutations in CFDI patients were evaluated using a published library of chaperone responsive mutations based on a HEK cell assay.
Results: We evaluated 404 FD patients with 143 males, 261 females, mean age 45.0±17.8 (sd), range 8-86 years; over 95% have been genotyped. Chaperone responsiveness mutations (n=23) was noted in 86 patients (21.3%); half were receiving ERT. Non-responsive mutations (n=67) were found in 318 patients (78.7%). Patients with chaperone responsive mutations had classic FD phenotype in 72.1%, vs. variant (24.4%) or indeterminate (3.5%) phenotypes. Chaperone responsive mutations varied by region: Alberta 25 patients (prevalence 48.1%) vs. Nova Scotia 2 patients (2.2%).
Conclusions: Oral PCT could be used in about one fifth of the current Canadian FD population. Restricting PCT to those that meet current ERT guidelines would only change treatment in about 40 (10%) FD patients in Canada. These data will help plan future therapy.
Keywords: Fabry disease, enzyme replacement therapy, pharmacologic chaperone therapy, prevalence
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