ACKNOWLEDGEMENTS

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Clara van Karnebeek, MD, PhD, FCCMG (Chair)
Associate Clinician Scientist, CFRI
Principal Investigator, Centre for Molecular Medicine and Therapeutics
Assistant Professor, Division of Biochemical Diseases, Department of Pediatrics, Faculty of Medicine, University of British Columbia

Lorne Clarke, MD, PhD, FRCPC
Professor, Department of Medical Genetics, University of British Columbia

Gabriella Horvath, MD, FRCPC, FCCMG
Clinical Assistant Professor, Department of Pediatrics Biochemical Diseases Clinic, University of British Columbia,
British Columbia Children's Hospital Adult Metabolic Diseases Clinic, Vancouver General Hospital

Anna Lehman, MD, FRCPC
Clinical Investigator, CFRI
Assistant Professor, Department of Medical Genetics, University of British Columbia
Clinical Geneticist, Provincial Medical Genetics Programme
Physician, Adult Metabolic Diseases Clinic, Vancouver General Hospital

André Mattmann, MD, FRCPC
Clinical Associate Professor, Department of Pathology, University of British Columbia, Medical Biochemist, Adult Metabolic Diseases Clinic, Vancouver General Hospital

Ramona Salvarinova, MD, FRCPC, FCCMG
Clinician, Division of Biochemical Diseases, BC Children's Hospital
Clinical Assistant Professor, Department of Pediatrics, University of British Columbia

Graham Sinclair, PhD, FCCMG
Biochemical Geneticist, Newborn Screening and Biochemical Genetics Laboratories BC Children's Hospital Clinical Associate Professor, Department of Pathology, University of British Columbia

Sandra Sirrs, MD, FRCPC
Clinical Associate Professor
Medical Director, Adult Metabolic Diseases Clinic
University of British Columbia

Sylvia Stockler, MD, PhD, MBA, FRCPC
Professor of Pediatrics
Head, Division of Biochemical Diseases
University of British Columbia Department of Pediatrics

Hilary Vallance, MD, FRCPC, FCCMG
Medical Biochemist and Director, Biochemical Genetics Laboratory, Children's & Women's Health Centre of British Columbia
Clinical Professor, Department of Pathology and Laboratory Medicine, University of British Columbia

Keiko Ueda, MPH, RD
Clinical Dietitian Specialist, Biochemical Diseases (Metabolism) Clinic, British Columbia Children's Hospital, Vancouver, British Columbia

Garrod Symposium 2015 Secretariat
garrodsymposium.com | info@garrodsymposium.com
+1-613-531-9210
4 Cataraqui Street, Suite 310, Kingston, ON K7K 1Z7

SOCIAL EVENTS

THURSDAY, MAY 21

Welcome Reception
1830–2200
Four Seasons Pool Deck
Sponsored by Actelion
Tickets: No charge for registered delegates; $40 for guests

FRIDAY, MAY 22

FlyOver Canada
1730–1830
Canada Place Pier, 999 Canada Place
Tickets: $20.00 per person
Meet in the Four Seasons hotel lobby at 1715 to catch the bus.

See Canada like never before at Vancouver's new must-see attraction! At its core, FlyOver Canada is a breathtaking, family-friendly, flight simulation ride like no other! You will take off into a huge dome screen with the latest in projection and ride technology creating a true flying experience (complete with wind, scents, and mist!).

The bus will pick up at the FlyOver venue at 1830 to return to the Four Seasons Hotel and to bring dinner attendees to the Vancouver Aquarium.

Garrod Symposium Annual Dinner & Entertainment
1900–2300
Vancouver Aquarium
Tickets: $90.00 per person
Meet in the Four Seasons hotel lobby at 1830 to catch the bus.

In the Teck Connections Gallery you'll find a variety of new animal exhibits that represent the diversity of aquatic life at the Aquarium. The centerpiece is a unique 14-foot globe which uniquely highlights the Arctic and is surrounded by 360 degrees of uninterrupted screens, taking you even deeper on your aquatic journey.

Important note about the entertainment at the aquarium: In 1996, Vancouver Aquarium became the first aquarium in the world to make a commitment to no longer capture cetaceans from the wild for display. They now only accept and care for whales, dolphins and porpoises (cetaceans) that were born in an aquarium or were rescued and deemed non-releasable by an appropriate government authority. The last whale or dolphin collected by the Aquarium happened over 20 years ago, in 1990. That same whale, Aurora, contributes to our knowledge of wild belugas, including ground breaking research, which investigates the impact of boat noise on beluga vocalizations and how it affects the ability of beluga moms and calves to call each other. This is especially important in light of the shrinking ice cover and impending increase in shipping traffic in the Arctic.

BUSINESS MEETINGS

THURSDAY, MAY 21

1230–1530.....Strathcona Room
Advisory Board Meeting (Invitation Only, includes lunch)
Sponsored by Medunik

1300–1500..... Montague Room
Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)

1500–1600..... Montague Room
Discussion: CPT1aP479L mutation in First Nations and Inuit Populations: Is current practice appropriate given current knowledge?

SATURDAY, MAY 23

1400–1600.....Strathcona Room
Garrod Association Membership Meeting

REGISTRATION DESK HOURS

The Registration desk is located in the Arbutus Foyer on the Third Floor. The desk will be open:

Thursday, May 21	0700-1900
Friday, May 22	0700-1800
Saturday, May 23	0800-1200

SCHEDULE AT A GLANCE

THURSDAY MAY 21		**ROOM**
0900–1230	Clinical application of –omics technologies in the newborn setting, includes lunch	Arbutus
1030–1230	Dietitians' Webinar	Montague
1230–1530	Advisory Board Meeting (Invitation Only), includes lunch	Strathcona
1300–1500	Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)	Montague
1500–1600	Discussion: CPT1aP479L mutation in First Nations and Inuit Populations: Is current practice appropriate given current knowledge?	Montague
1600–1815	Progress & Challenges in Recognizing Inborn Errors of Metabolism Presenting with Neuropsychiatric Symptoms	Arbutus
1830–2200	Welcome Reception	Pool Deck

FRIDAY MAY 22		
0700–0815	Hypophosphatasia: The Significance and the Consequences of Low Alkaline Phosphatase, Includes Breakfast	Seasons
0830–1030	Neuro-Metabolic Movement Disorders	Arbutus
1030–1100	Refreshment Break	Arbutus Foyer
1100–1230	Adult Metabolic Diseases & Transitions	Arbutus
1230–1330	Emerging Issues in the Management of Morquio A	Pavillon
1345–1600	New Discoveries/New Approaches	Arbutus
1600–1700	Poster Walk and Presentations	Oak & Aspen
1730–1830	FlyOver Canada *Meet in the Four Seasons Hotel lobby at 1715 to catch the bus*	Offsite
1900–2300	Garrod Symposium Annual Dinner & Entertainment at the Vancouver Aquarium *Meet in the Four Seasons Hotel lobby at 1830 to catch the bus*	Offsite

SATURDAY MAY 23		
0800–0900	Light Breakfast	Arbutus Foyer
0900–1030	Collaborative Discovery, Emerging Therapies, More Evidence (Part I)	Arbutus
1030–1100	Refreshment Break	Arbutus Foyer
1100–1215	Collaborative Discovery, Emerging Therapies, More Evidence (Part II)	Arbutus
1230–1345	The Canadian Orphan Drug “Framework” in Context. Implications for Patients, Practice, & Society, includes lunch	Arbutus
1400–1600	Garrod Association Membership Meeting	Strathcona

POSTER PRESENTATIONS

Posters will be mounted on Friday morning by 0800. Posters can viewed during all breaks and lunch breaks. The Poster Walk will take place on Friday afternoon at 1600–1700, and presenters will be attending their posters at that time.

THURSDAY MORNING | 0900–1230

Clinical application of –omics technologies in the newborn setting

Time 0900–1230 (includes lunch)
Room Arbutus

Moderators **Clara van Karnebeek**, MD, PhD, University of British Columbia
Jan Friedman, MD, PhD, University of British Columbia

0900–0905 **Welcome & Introductions**

0905–0945 **Clinical and social implications of 2-day genome results in acutely ill newborns**
Stephen Kingsmore, MB, ChB, BAO, DSc, Medical Panomics; University of Missouri-Kansas City School of Medicine

0945–1000 **Q&A**

1000–1020 Refreshment Break

1020–1045 **Successful development and application of semi-automated gene-discovery NGS bioinformatics pipeline: Knowledge gained through Omics2TreatID**
Maja Tarailo, PhD, University of British Columbia

1045–1110 **Metabolomics and its application in the newborn period**
Pranesh Chakraborty, MD, University of Ottawa

1110–1135 **Challenges and implications of sequencing newborns: Ethical, Legal, Social Issues**
Shelin Adam, BSc, MSc, University of British Columbia

1135–1200 **Panel discussion**

1200–1230 **Lunch**

Sponsored by: PerkinElmer For the Better

Dietitians' Webinar

Time 1030–1230
Room Montague

1030–1110 **Use of novel and minimally invasive techniques to measure protein requirements and phenylalanine metabolism in children with PKU**
Rajavel Elango, PhD, University of British Columbia

1110–1200 **Glutaric Acidemia type 1**
Cheryl Rockman-Greenberg, MD, CM, Winnipeg Children's Hospital; University of Manitoba

1200–1215 **Glutaric acidemia type 1 adult patient case study**
Annie Rosen Heath, RD, Vancouver General Hospital Adult Metabolic Clinic

1215–1230 **Q&A / Ask the speakers: webinar participant group discussion**

Sponsored by: CAMBROOKE THERAPEUTICS

THURSDAY AFTERNOON | 1230–1600

Advisory Board Meeting (Invitation Only)

Time 1230–1530 (includes lunch)
Room Strathcona
Sponsored by: Mēdunik Canada

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

Time 1300–1500
Room Montague

Discussion: CPT1aP479L mutation in First Nations and Inuit Populations: Is current practice appropriate given current knowledge?

Time 1500–1600
Room Montague

Chair **Cheryl Rockman-Greenberg**, MD, CM, WRHA and University of Manitoba

Introduction

Overview of the CPT1A P479L mutation in First Nations and Inuit aboriginal populations
Laura Arbour, MD, University of Victoria

- Frequency across different regions in Canada and circumpolar areas
- The evidence (if any) for association of P479L with
  - increased morbidity (hypoglycemia, seizures, infection)
  - increased mortality (SIDS and SUDS)Key knowledge gaps

Review of current practices: ascertainment (clinical /NBS), medical guidelines and public messaging in BC, MB and ON
BC: Hilary Vallance, MD, University of British Columbia
MB: Cheryl Rockman-Greenberg, MD, CM, WRHA and University of Manitoba
ON: Pranesh Chakraborty, MD, University of British Columbia

Discussion

- What are priorities for research?
- Is current practice appropriate given current knowledge?
- Some key metabolic points
  - CPT1A is expressed in the liver, kidney, brain, pancreas, leukocytes, fibroblasts, and embryonic tissues whereas CPT1B is found in muscle and heart, and brown adipose tissue (Bonnefont et al. 2004). CPT1C is restricted to the CNS and its exact role is still unclear (Sierra et al. 2008)
  - CPT1A is the rate limiting enzyme for mitochondrial FAO
  - Impact of the P479L on in vitro FAO in health and illness
- Is P479L mutation linked to the high frequency of respiratory infection and otitis media seen in Inuit children and, if so, is it through effect of P479L on T cell function? i.e. do babies with P479L have altered immune function predisposing to respiratory infection?
- Is the increased risk for infection mediated through P479L and could this thus be the main driver for increased morbidity in Inuit children?

Next steps

THURSDAY AFTERNOON | 1600–2200

Progress and Challenges in Recognizing Inborn Errors of Metabolism Presenting with Neuropsychiatric Symptoms

Time 1600–1815
Room Arbutus

1600–1615 **Inborn Errors of Metabolism (IEM) with Neuropsychiatric Presentation – An Overview of the challenges and progress to date**
Clara van Karnebeek, MD, PhD, University of British Columbia

1615–1635 **Differential Diagnosis – Rare or Rarely Diagnosed? Genetic Syndromes in Psychiatry**
Joyce So, MD, PhD, University Health Network

1635–1655 **Massively Parallel Sequencing as a First-Tier Clinical Diagnostic Test for Disorders with Overlapping Neuropsychiatric Phenotypes**
Sébastien Lévesque, M., PhD, Centre Hospitalier Universitaire de Sherbrooke

1655–1735 **Neuropsychiatric Manifestations of Niemann-Pick Disease Type C: An Evolving Picture**
Marc Patterson, MD, Mayo Clinic

1735–1755 **Oxysterols – New Biomarkers for the Detection of NP-C**
Daniel Ory, MD, Washington University

1755–1805 **Think Again: An Awareness Campaign About NP-C for Canadian Healthcare Professionals**
Tammy Vaughan, Canadian Chapter of the Niemann-Pick Disease Foundation

1805–1815 **Closing Remarks**
Clara van Karnebeek, MD, PhD, University of British Columbia

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WELCOME RECEPTION
Pool Deck at the Four Seasons Hotel
1830–2200

Sponsored by:

ACTELION

FRIDAY MORNING | 0700–1100

Hypophosphatasia: The Significance and the Consequences of Low Alkaline Phosphatase

Time 0700–0815 (including breakfast)
Room Seasons

Speaker **Cheryl Rockman-Greenberg**, MD, CM, WRHA and University of Manitoba

Objectives At the end of this session the participant will be able to:

- Discuss the pathophysiology of hypophosphatasia and the role of alkaline phosphatase.
- Recognize the systemic consequences of low alkaline phosphatase activity.
- Evaluate biochemical and radiological tests in diagnosis of hypophosphatasia.

Sponsored by: ALEXION

GARROD SYMPOSIUM | 0830–1100

Welcome & Introductions

Time 0830–0835
Room Arbutus

Clara van Karnebeek, MD, PhD, Chair Garrod 2015 Committee

Neuro-Metabolic Movement Disorders

Time 0835–1030
Room Arbutus

Moderators **Clara van Karnebeek**, MD, PhD, University of British Columbia
Ramona Salvarinova, MD, University of British Columbia

0835–0915 **Movement Disorders in Neurometabolic Diseases**
Birgit Assmann, MD, University Children's Hospital Heidelberg

Objectives At the end of this session the participant will be able to:

- Diagnose a pyramidal movement pattern.
- Diagnose a dystonic movement pattern.
- Diagnose a choreatic movement pattern.
- Diagnose a cerebellar movement pattern.
- Evaluate some treatment options.

0915–0945 **Neuro–Metabolic Movement Disorders**
Nenad Blau, PhD, University Children's Hospital Heidelberg

Objectives At the end of this session the participant will be able to:

- Discuss biochemical pathways of biogenic amine.
- Explain differences in biochemical patterns.
- Interpret biochemical laboratory data.

0945–1030 **Platform Presentations of selected abstracts**

0945–1000 **Abnormal neurotransmitter metabolite profiles in pediatric epilepsy: single academic institution experience and review of the literature**
Mary Dunbar MD, University of British Columbia.

1000–1015 **Triple therapy (Arginine fortification + Lysine Restricted Diet + Pyridoxine) for pyridoxine dependent epilepsy**
Sravan Jaggumantri BSc, Treatable Intellectual Disability Endeavour in British Columbia (TIDE-BC), Division of Biochemical Diseases, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver.

1015–1030 **Quantification of glutarylcarnitine, 3-hydroxyglutaric and glutaric acid in dried urine spots for the diagnostic workup of glutaric aciduria type 1**
Osama Y. Al-Dirbashi PhD, Newborn Screening Ontario, Children's Hospital of Eastern Ontario, Ottawa. Children's Hospital of Eastern Ontario Research Institute, Ottawa. Department of Pediatrics, University of Ottawa, Ottawa.

1030–1100 **Refreshment Break**

FRIDAY MORNING & LUNCH | 1100–1330

Adult Metabolic Diseases & Transitions

Time 1100–1230
Room Arbutus

Moderator **Lorne Clarke**, MD, PhD, University of British Columbia

1100–1130 **Adult Metabolic Diseases & Transitions**
Sandra Sirrs, MD, University of British Columbia

Objectives At the end of this session the participant will be able to:

- Define transition as it applies to patients with metabolic diseases.
- List elements of a successful transition process.
- Describe barriers to transition as they apply to patients with metabolic diseases.
- List potential resources to enhance transition planning.

1130–1230 **Platform Presentations of selected abstracts**

1130–1145 **The Canadian Inherited Metabolic Diseases Research Network: Initial findings from a pan-Canadian longitudinal study of affected children**
Jonathan B. Kronick MD, Hospital for Sick Children/University of Toronto, Toronto, Ontario.

1145–1200 **18-Month results from the Eliglustat ENGAGE Phase 3 trial in treatment-naïve adults with Gaucher Disease Type 1**
Thomas Andrew Burrow MD, Cincinnati Children's Hospital Medical Center.

1200–1215 **MiMo: "from bed to bench to health" – An integrated translational approach to mitochondrial diseases**
Catherine Brunel-Guitton MD, Division of Medical Genetics, Department of Pediatrics & Biochemical Genetics Diagnostic Laboratory, CHU Sainte-Justine, University of Montreal, Montreal, Quebec.

1215–1230 **Outpatient human Hemin (Normosang®) therapy for acute intermittent porphyria**
Chitra Prasad MD, Western University. London Health Sciences Centre.

LUNCH 1230–1330

Emerging Issues in the Management of Morquio A

Time 1230–1330
Room Pavillon

Speakers: **Lorne Clarke**, MD, PhD, University of British Columbia
John Mitchell, MD, Montreal Children's Hospital
Julian AJ Raiman, MB BS MSc MRCP(UK), University of Toronto

Objectives

- Understand the surveillance and monitoring of patient spectrums from under 5 years of age to adult, ambulant and non-ambulant patients with Morquio A.
- An update on the MPS IVA/Morquio A Management Guidelines and Canadian Expert Opinion Statement for The Management of Morquio A.
- Discuss emerging issues of puberty and pregnancy in Morquio A patients.
- Update on the Canadian Reimbursement Landscape for Vimizim.

Sponsored by: BIOMARIN

FRIDAY AFTERNOON | 1345–1700

New Discoveries/New Approaches

Time 1345–1600
Room Arbutus

Moderators **Sylvia Stockler**, MD, PhD, MBA, University of British Columbia
André Mattmann, MD, University of British Columbia

1345–1400 **A personal introduction to Rabenoysn-5 deficiency**
Sylvia Stockler, MD, PhD, MBA, University of British Columbia & the **Davis Family**

1400–1430 **Metabolic Medicine in Motion**
Silvia Corvera, MD, University of Massachusetts Medical School

Objectives At the end of this session the participant will be able to:
- List the major proteins that participate in early endosome trafficking.
- List the five different functional motifs in the protein Rabenosyn–5.
- Compare the functional motifs of the proteins Rabenosyn–5 and EEA1.
- Discuss the possible consequences to the cell of disruption of Rabenosyn–5 function.

1430–1500 **Endosomal Trafficking & Recycling in Health and Genetic Disease**
Elizabeth Conibear, PhD, University of British Columbia

Objectives At the end of this session the participant will be able to:
- Name at least three neurological diseases linked to endosomal defects.
- Discuss how a systems biology approach can be used to prioritize gene variants.
- Describe how model organisms such as budding yeast can be used for the identification and functional validation of candidate disease genes.

1500–1600 **Platform Presentations of selected abstracts**

1500–1515 **Acylglycine profiling: a new liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, applied to disorders of organic acid, fatty acid and ketone metabolism**
Paula J. Waters PhD, Medical Genetics Service, Department of Pediatrics, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, QC.

1515–1530 **The 3' addition of CCA to mitochondrial tRNASer(AGY) is specifically impaired in patients with mutations in the tRNA nucleotidyl transferase TRNT1**
Florin Sasarman PhD, Montreal Neurological Institute and Department of Human Genetics, McGill University, Montreal, Canada. Division of Medical Genetics, Department of Pediatrics, CHU Sainte-Justine and Université de Montréal, Montreal, Canada.

1530–1545 **NANS deficiency: first discovery of a novel inborn error of metabolism by a combined high throughput metabolic screening & genomics approach**
Clara van Karnebeek MD PhD, BC Children's Hospital.

1545–1600 **FLAGS: candidate gene prioritization scheme based on frequently mutated genes in public exomes**
Casper Shyr PhD, Centre for Molecular Medicine and Therapeutics; Child and Family Research Institute, Vancouver BC, Canada. Treatable Intellectual Disability Endeavour in British Columbia (www.tidebc.org), Vancouver, Canada. Bioinformatics Graduate Program, University of British Columbia, Vancouver BC, Canada.

POSTER WALK | 1600–1700
Oak Room and Aspen Room
(all presenters to attend their posters)

FRIDAY EVENING | 1730–2300

FlyOver Canada
1730–1830
Canada Place Pier, 999 Canada Place
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See Canada like never before at Vancouver's new must-see attraction! At its core, FlyOver Canada is a breathtaking, family-friendly, flight simulation ride like no other! You will take off into a huge dome screen with the latest in projection and ride technology creating a true flying experience (complete with wind, scents, and mist!).

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Vancouver Aquarium
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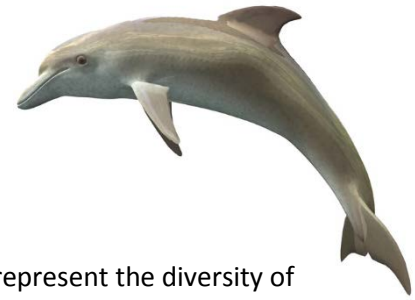

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GARROD 2015 AWARD PRESENTATION AND LECTURE
The Garrod 2015 Award will be presented to
Dr. Derek Applegarth, Emeritus Professor, University of British Columbia

SATURDAY MORNING & LUNCH | 0800–1345

Light Breakfast

Time 0800–0900
Room Arbutus Foyer

Collaborative Discovery, Emerging Therapies, More Evidence

Time 0900–1215
Room Arbutus

Moderators **Graham Sinclair**, PhD, University of British Columbia
Hilary Vallance, MD, University of British Columbia

0900–0930 **Understanding Rare Disease Pathogenesis: A Grand Challenge for Model Organisms**
Philip Hieter, PhD, University of British Columbia

Objectives At the end of this session the participant will be able to:
- Highlight the variety of strategies and power of model organisms to elucidate human disease mechanisms.
- Highlight the value of model organisms for discovering and evaluating novel treatment approaches for genetic disease.
- Highlight the value of collaboration between clinicians, clinician scientists, and basic researchers.

0930–1000 **Novel Therapeutic Approaches for Rare Genetic Disease; After the Deluge**
Alex MacKenzie, MD, PhD, CHEO Research Institute

Objectives At the end of this session the participant will be able to:
- Appreciate unmet medical need of rare diseases.
- Develop understanding of generalizable approaches for rare diseases.
- Understand pharmacologic modulation of gene expression.

1000–1030 **Platform Presentations of selected abstracts**

1000–1015 **GeneYenta: A phenotype-based rare disease case matching tool based on online dating algorithms for the acceleration of exome interpretation**
Michael M. Gottlieb BSc, Graduate Program in Bioinformatics, University of British Columbia, Vancouver, British Columbia, Canada.

1015–1030 **OMICS2TREATID: A collaborative approach to accelerate the discovery of rare neuro-metabolic diseases**
Maja Tarailo-Graovac PhD, Centre for Molecular Medicine and Therapeutics, Vancouver, Canada. Department of Medical Genetics, University of British Columbia, Vancouver, Canada. Treatable Intellectual Disability Endeavour in British Columbia (www.tidebc.org), Vancouver, Canada.

1030–1100 **Refreshment Break**

1100–1130 **Discovery in IEMs: Translation into Clinical Care**
Marc Patterson, MD, Mayo Clinic

Objectives At the end of this session the participant will be able to:
- Discuss challenges in designing clinical trials in IEMs.
- Summarize the basics of regulatory requirements for drug approval.
- Explain why standard clinical trial designs may not be appropriate for IEMs.
- Explain the importance of natural history studies and validated biomarkers in clinical trials in IEMs.

1130–1215 **Platform Presentations of selected abstracts**

1130–1145 **The metabolic diet app suite: medical diets made easier using digital technologies**
Gloria Ho BSc, Division of Biochemical Disease / TIDE-BC, Department of Pediatrics, B.C. Children's Hospital, Vancouver, B.C.

Continued next page

1145–1200 **N-of 1 study with oral S-adenosyl methionine as adjunct to L-arginine, glycine and creatine supplements for treatment of creatine transporter (SLC6A8) deficiency**
Sravan Jaggumantri BSc, Division of Biochemical Diseases (TIDE-BC), Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, Canada. Child and Family Research Institute, University of British Columbia, Vancouver, Canada.

1200–1215 **Sapropterin-responsiveness testing in PKU patients: the Calgary Metabolic Clinic approach**
Rebecca L. Sparkes M.D., Inherited Metabolic Disorders Clinic, Alberta Children's Hospital, Calgary, AB. Department of Medical Genetics, Cumming School of Medicine, University of Calgary, Calgary, AB. Alberta Health Services.

Closing of the Garrod Symposium

Time 1215
Room Arbutus

Clara van Karnebeek, MD, PhD, University of British Columbia

LUNCH 1230–1345

The Canadian Orphan Drug "Framework" in Context. Implications for Patients, Practice, and Society

Time 1230–1345
Room Arbutus

Speaker: **Larry Lynd**, PhD, BSP, University of British Columbia

Objectives At the end of this session the participant will be able to:

- Outline the key components of the Canadian Orphan Drug framework in the context of the international orphan drug policy.
- Discuss the implications of the Canadian framework as they relate to current legislation in other countries.
- Explore the relationship between orphan drug policy and legislation with patient access to effective therapies and the development or new treatments.

Sponsored by: Shire

GARROD ASSOCIATION MEMBERSHIP MEETING | 1400–1600
Strathcona Room

ABSTRACTS

PLATFORM PRESENTATIONS

Friday May 22, 0945–1000

Abnormal neurotransmitter metabolite profiles in pediatric epilepsy: single academic institution experience and review of the literature

Mary Dunbar[a], Clara van Karnebeek[a], Csilla Egri[b], Bryan Sayson[a], Sylvia Stockler-Ipsiroglu[b], Mary Connolly[a], Gabriella Horvath[b].
[a]University of British Columbia. [b]BC Children's Hospital.

Objective: Neurotransmitter deficiencies secondary to medical or genetic disease are an emerging area of interest. The relationship between epilepsy and neurotransmitter abnormalities has not been well defined. Our goal was to explore the correlations between epilepsy, movement disorders, MRI abnormalities and secondary neurotransmitter deficiency.

Study Design: Retrospective case series of 636 patients who underwent neurotransmitter analysis at BC Children's Hospital during intervals (2003-2007 and 2009-2013) for a variety of neurological presentations. The biochemical genetics laboratory database was interrogated for results of cerebrospinal fluid neurotransmitter analyses. Clinical data for patients with abnormal results were collected from the hospital charts. A more detailed clinical review was performed on the 2009-13 patients. Statistical analysis included one-way ANOVA, chi-square and 2-way contingency table.

Results: Abnormal neurotransmitter values were identified in 118 patients, 7 of which were attributable to primary neurotransmitter deficiency. Of the remaining 111 patients, 72 (64.8%) presented with epilepsy. Of 69 patients with abnormal neurotransmitter values (analyzed 2009-2013), 43 (62.3%) presented with epilepsy and 20 (28.9%) with movement disorders. A combination of seizure and movement disorder was significantly less frequent.

Conclusions: Epilepsy and epileptic encephalopathy are found commonly in association with secondary neurotransmitter abnormalities in addition to movement disorders, however there is no clear relation between clinical phenotype and type of neurotransmitter affected. In addition, no association was identified between the type of anti-seizure medications and affected neurotransmitter type. Notable, a subset of patients with secondary neurotransmitter abnormalities can benefit from replacement therapy, with improved seizure control.

Keywords: Neurotransmitter, epilepsy, serotonin, dopamine, movement disorder

Funding: This study was supported by the BC Children's Hospital Foundation, as part of the "1st Collaborative Area of Innovation".

Friday May 22, 1000–1015

Triple therapy (Arginine fortification + Lysine Restricted Diet + Pyridoxine) for pyridoxine dependent epilepsy

Curtis R Coughlin II[a], Clara D.M. van Karnebeek[b], Sravan Jaggumantri[b], Walla Al-Hertani[c], Andrew Y. Shuen[c], Rhona M. Jack[d], Sommer Gaughan[a], Casey Burns[a], Renata C. Gallagher[a,f], David M. Mirsky[e], Johan L.K. Van Hove[a].
[a]Section of Clinical Genetics and Metabolism, Department of Pediatrics, University of Colorado, Aurora, CO, United States. [b]Treatable Intellectual Disability Endeavour in British Columbia (TIDE-BC), Division of Biochemical Diseases, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, Canada. [c]Department of Medical Genetics, Montreal Children's Hospital, McGill University of Health Centre, Montreal, Canada. [d]Department of Laboratory Medicine, Seattle Children's Hospital Laboratory, Seattle, WA, United States. [e]Department of Radiology, University of Colorado, Aurora, CO United States. [f]Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco, CA, United States.

Introduction: Pyridoxine dependent epilepsy (PDE) is an epileptic encephalopathy caused by mutation in *ALDH7A1* gene resulting in impaired cerebral lysine catabolism and accumulation of neurotoxic metabolites. Despite adequate seizure control with pyridoxine, 80% of individuals with PDE have significant developmental delay and intellectual disability.

Objectives: To evaluate the effect of triple therapy on biomarkers and neurodevelopmental outcome in patients with pyridoxine dependent dpilepsy (PDE) due to ATQ deficiency.

Design and Methods: We conducted an open label observational cohort study in 6 PDE patients on triple therapy (Arginine fortification - 150mg/kg/day, Lysine restricted diet – as per PDE consortium guidelines and pyridoxine -15-30mg/kg/day) for 6-12 months. Neurodevelopmental outcome was measured using, standard scales along with level of plasma, urine and cerebrospinal fluid (CSF) biomarkers.

Results: Triple therapy was well tolerated and safe. Patients on triple therapy showed near normalization of urine α-aminoadiphic semialdehyde and plasma pipecolic acid. Level of biomarkers in CSF further decreased after arginine fortification in patients already on lysine restricted diet. All patients showed improvement in developmental and cognitive domains, specifically in motor skills and speech; younger patients seemed to benefit most. Furthermore, a decrease in calculated brain lysine influx was noted.

Conclusion: Decreasing brain lysine flux via dietary restriction and arginine supplementation (competitive inhibition over the blood-brain-barrier) is effective in decreasing neurotoxic metabolite production and improving cognitive function. Further studies are needed to generate more robust evidence and elucidate optimal treatment. Early diagnosis via newborn and neonatal screening allow for early intervention and potentially improved cognitive outcomes.

Friday May 22, 1015–1030

Quantification of glutarylcarnitine, 3-hydroxyglutaric and glutaric acid in dried urine spots for the diagnostic workup of glutaric aciduria type 1

Osama Y. Al-Dirbashi[a,b,c], Amy Chambers[a], Nathan McIntosh[a], Michael T. Geraghty[c], Murray Potter[d], Chitra Prasad[e], Tony Rupar[e], Andreas Schulze[f], David Sinasac[g], Graham Sinclair[h], Pranesh Chakraborty[a,b,c].
[a]Newborn Screening Ontario, Children's Hospital of Eastern Ontario, Ottawa. [b]Children's Hospital of Eastern Ontario Research Institute, Ottawa. [c]Department of Pediatrics, University of Ottawa, Ottawa. [d]Department of Pathology and Molecular Medicine McMaster University, Hamilton. [e]London Health Sciences Centre, London. [f]Hospital for Sick Children, Toronto. [g]Dept. of Medical Genetics, University of Calgary, Calgary. [h]BC Children's Hospital, Vancouver.

Glutaric Aciduria type 1 (GA1) is an autosomal recessive defect in the metabolic pathway of lysine, hydroxylysine and tryptophan. Most newborns with GA1 appear normal, but can be identified through newborn screening. To avoid false negatives, screening laboratories apply conservative glutarylcarnitine (C5DC) cutoffs leading to increased false positive rates. Newborns triggering positive GA1 results or clinically suspected patients receive comprehensive investigation to clarify their disease status. This involves quantification of biochemical hallmarks, glutaric acid (GA) and 3-hydroxyglutaric acid (3HGA), which are traditionally measured by stable isotope dilution GC-MS, a method limited to small number of expert labs. Recently, we described an LC-MS/MS method to quantify these markers in dried urine spots (DUS).The method was validated using DUS from genetically confirmed patients (n=18).

Over the past 4 years we prospectively tested > 80 DUS specimens for C5DC, GA and 3HGA as part of the diagnostic workup for GA1. While the majority of these samples produced normal results, a few (n=4) were consistent with GA1 including low and high excretor phenotypes. Interestingly a fifth sample with elevated GA and normal 3HGA and C5DC was confirmed later to be GA type 3. Our method was also applied to evaluate these markers in DUS (n=18) from newborns with GA1 in a retrospective study.

The value of this approach is apparent in the convenience of collecting and shipping DUS and the ability of obtaining fast and reliable information to assist in making the decision of whether to proceed with further complex and invasive testing.

Friday May 22, 1130–1145

The Canadian Inherited Metabolic Diseases Research Network: Initial findings from a pan-Canadian longitudinal study of affected children

Jonathan B. Kronick[a], Beth K. Potter[b], Pranesh Chakraborty[b,c], Monica Lamoureux[c], Kylie Tingley[b], Doug Coyle[b], Kumanan Wilson[b], Valerie Austin[a], Catherine Brunel[d], Daniela Buhas[e], Maggie Chapman[f], Alicia K.J. Chan[g], Sarah Dyack[f], Annette Feigenbaum[a], Michael Geraghty[b,c], Alette Giezen[h], Jane Gillis[f], Shailly Jain[g], Aneal Khan[i], Erica Langley[c], Julian Little[b], Jennifer MacKenzie[j], Bruno Maranda[k], Aizeddin Mhanni[l], Grant Mitchell[d], John J. Mitchell[e], Laura Nagy[a], Amy Pender[m], Murray Potter[m], Chitra Prasad[n], Komudi Siriwardena[a], Rebecca Sparkes[i], Sylvia Stockler[h], Yannis Trakadis[e], Lesley Turner[o], Clara Van Karnebeek[h], Hilary Vallance[h], Jagdeep Walia[j], Brenda Wilson[b], on behalf of the Canadian Inherited Metabolic Diseases Research Network (CIMDRN).

[a]Hospital for Sick Children/University of Toronto, Toronto, Ontario. [b]University of Ottawa, Ottawa, Ontario. [c]Children's Hospital of Eastern Ontario, Ottawa, Ontario. [d]CHU Ste-Justine, Montreal, Quebec. [e]McGill University/Montreal Children's Hospital, Montreal, Quebec. [f]Dalhousie University/IWK Health Centre, Halifax, Nova Scotia. [g]University of Alberta, Edmonton, Alberta. [h]University of British Columbia/BC Children's Hospital, Vancouver, British Columbia. [i]University of Calgary/Alberta Children's Hospital, Calgary, Alberta. [j]Queen's University/Kingston General Hospital, Kingston, Ontario. [k]University of Sherbrooke/CHU Sherbrooke, Sherbrooke, Quebec. [l]University of Manitoba/HSC Winnipeg, Winnipeg, Manitoba. [m]McMaster University, Hamilton, Ontario. [n]Western University/LHSC London, London, Ontario. [o]Memorial University/Janeway Children's Health Centre, St. John's, Newfoundland.

Objectives: The Canadian Inherited Metabolic Diseases Research Network (CIMDRN) is a practice-based research network designed to develop evidence needed to improve outcomes for children with inborn errors of metabolism (IEM).

Design and Methods: As part of CIMDRN's clinical research stream, we are enrolling Canadian children (born between 2006 and 2015 and diagnosed with one of 30 targeted IEM). The clinical database, hosted on Research Electronic Data Capture (REDCap), collects retrospective and prospective information from participants' medical charts. The data include clinical descriptors and indicators of prognosis, interventions received and potential modifiers of intervention effectiveness, clinical outcomes, and intermediate indicators of disease management.

Results: Patient recruitment is currently occurring at 8 of the 14 participating Treatment Centres within the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, and Nova Scotia. To date (February 2015), 177 children have been enrolled, with data entered for 175 participants (8 deceased). CIMDRN participants' diagnoses include 23 of CIMDRN's 30 target diseases – phenylalanine hydroxylase deficiency (n=63), other amino acid disorders (n=10), medium-chain acyl-CoA dehydrogenase deficiency (n=34), other fatty acid oxidation disorders (n=17), urea cycle disorders (n=11), organic acid disorders (n=16), and other IEM (n=24). CIMDRN's cohort is 54% male and age ranges (of n=171 non-deceased participants with data entered) are: <=1 year (n=32), 2-3 years (n=48), 4-5 years (n=38), >=6 years (n=57).

Conclusions: We have established a rich and sustainable dataset and have begun analyses to generate the practice-based evidence needed to overcome critical challenges of clinical longitudinal research toward improved care and outcomes for IEM.

Keywords: inborn errors of metabolism, long-term follow up, practice-based evidence

Funding: Canadian Institutes of Health Research (CIHR) [Grant # TR3-119195]

Friday May 22, 1145–1200

18-Month results from the Eliglustat ENGAGE Phase 3 trial in treatment-naïve adults with Gaucher Disease Type 1

Thomas Andrew Burrow[a], Pramod Mistry[b], Dominick Amato[c], Majed Dasouki[d], Seymour Packman[e], Gregory Pastores[f], Sarit Assouline[g], Manisha Balwani[c], Andres Ortega[h], Suma Shankar[i], Maria Helena Solano[j], Leorah Ross[k], Jennifer Angell[k], Judith M Peterschmitt[l].

[a]Cincinnati Children's Hospital Medical Center. [b]Yale University School of Medicine. [c]Mount Sinai Hospital. [d]University of Kansas Hospital. [e]UCSF School of Medicine. [f]New York University School of Medicine. [g]Jewish General Hospital. [h]OCA Hospital, Monterrey, Mexico. [i]Emory University, Atlanta, GA, USA. [j]Hospital de San Jose-Fundacion de Ciencias de la Salud, Bogota, Colombia. [k]Genzyme, a Sanofi Company. [l]GE.

Introduction: Eliglustat, a ceramide analogue, is a novel oral substrate-reduction therapy approved in the United States, Europe, and Australia for Gaucher disease type 1 (GD1). We present 18-month results from ENGAGE (NCT00891202, Genzyme, a Sanofi company), a randomized, double-blind, placebo-controlled, Phase-3 trial investigating the efficacy and safety of eliglustat in untreated adults with GD1.

Methods: Forty adults with splenomegaly and thrombocytopenia and/or anemia were randomized 1:1 to receive eliglustat or placebo for 9 months followed by a 9-month open-label extension in which all patients received eliglustat. The primary efficacy endpoint was percent change in spleen volume (multiples of normal). Other efficacy measures included hemoglobin concentration, liver volume, platelet count, and bone measures.

Results: In the 9-month primary analysis period (PAP), eliglustat was superior to placebo in all primary and secondary endpoints; no patients discontinued due to an adverse event (Mistry. JAMA 2015;313:695). For 18/20 patients who received 18 months of eliglustat, mean improvements from baseline continued (spleen volume:. -45%, hemoglobin: +1.02 g/dL; liver volume: -11%; platelets: +58%) and mean bone marrow burden scores decreased from10.85 to 8.67. For 20/20 former placebo patients, mean improvements after 9 months of eliglustat were consistent with those seen in the PAP in eliglustat-treated patients: spleen: -31%; hemoglobin: +0.79 g/dL; liver: -7.3%; platelets: +40%. No new safety concerns were identified.

Conclusions: ENGAGE met its primary and secondary efficacy endpoints. Patients from both treatment arms showed continued improvements in spleen volume, haemoglobin, live volume, and platelets in the first 9 months of the extension phase.

Friday May 22, 1200–1215

MiMo: "from bed to bench to health" – An integrated translational approach to mitochondrial diseases

Catherine Brunel-Guitton MD[a], Pierre Allard PhD[a], Florin Sasarman PhD[a], Grant Mitchell MD[b], Jean-François Soucy MD[b], Julie Gauthier PhD[b], Jacques Michaud MD[b], Benjamin Ellezam MD[c], Bernard Brais MD[b], Eric A. Shoubridge PhD[d].

[a]Division of Medical Genetics, Department of Pediatrics & Biochemical Genetics Diagnostic Laboratory, CHU Sainte-Justine, University of Montreal, Montreal, Quebec. [b]Division of Medical Genetics, Department of Pediatrics & Molecular Genetics Diagnostic Laboratory, CHU Sainte-Justine, University of Montreal, Montreal, Quebec. [c]Department of Pathology, CHU Sainte-Justine and University of Montreal, Montreal, Quebec. [d]Montreal Neurological Institute (MNI), McGill University, Montreal, Quebec.

Objectives: Mitochondrial diseases are chronic, severe, progressive and can affect any organ. Few specific treatments are available. The largest subgroup of metabolic diseases, mitochondrial diseases cause deficiencies of oxidative phosphorylation (OXPHOS). With >1000 potential disease genes, mitochondrial diseases are clinically and genetically complex. We adopted a multidisciplinary, translational strategy, creating MiMo (Mitochondria Montreal), a working group that integrates clinical, diagnostic and research activities with the goal of better understanding energy metabolism for effective diagnosis and treatment of mitochondrial diseases.

Design and Methods: MiMo builds on long-term experience in clinical diagnosis and mitochondrial biology. Pediatric and adult patients are followed in a structured multidisciplinary fashion. The new mitochondrial platforms offer integrated diagnostic services. The biochemical genetics diagnostic laboratory offers Blue Native-PAGE

analysis of assembly of the five OXPHOS complexes in muscle and fibroblasts and enzymatic activity assay each OXPHOS complex, plus combined activity of Complexes II and III as an indirect measure of CoQ deficiency, in fresh and frozen muscle and in fibroblasts. The molecular genetics diagnostic lab will offer mitochondrial DNA sequencing, deletion/duplication analysis and clinical whole exome sequencing. Clinical, pathological, biochemical and molecular data are compiled in a patient database and discussed at MiMo workshops four times a year. Selected candidate genes are pursued further in research.
Results: MiMo has identified, validated and explained the function of 6 new disease genes.
Conclusions: An integrated approach can help unravel the complexity of mitochondrial disease through diagnosis and potentially through the development of new therapeutic avenues in the future.
Keywords: Mitochondrial diseases, Blue Native- PAGE, OXPHOS, Mitochondrial DNA sequencing, Whole exome sequencing
Funding: Funding from La Fondation du Grand défi Pierre Lavoie.

Friday May 22, 1215–1230

Outpatient human Hemin (Normosang®) therapy for acute intermittent porphyria

Chitra Prasad[a,c], Melanie Napier[b], Akshya Vasudev[c], Tony Rupar[c].
[a]Western University. [b]Children's Health Research Institute 3Department. [c]London Health Sciences Centre.

Background and objectives: Acute intermittent porphyria (AIP) remains an orphan disorder. With the advent of heme therapy there have been some beneficial effects in abdominal pain, peripheral neuropathy and neuropsychiatric symptoms. To date, this therapy is only provided for inpatients in Ontario and other provinces in Canada.
Case report: Our metabolic clinic follows approximately 10 patients with AIP. Of these patients, three of them (a 52-year old male with an R225X mutation in the HMBS gene, and two female first cousins, 36 and 38-years of age with an R173W mutation) have been receiving Normosang® once every two weeks as outpatient therapy.
Results: Prior to initiation of Heme therapy our male patient was hospitalized approximately twelve times per year with acute symptoms of abdominal pain and psychiatric etiology. Initially, he was started on 250 mg Normosang® every month, for 18-months duration, for 3-4 days as an inpatient. For the past ten months he has been receiving prophylactic Normosang® as an outpatient at 250 mg every two weeks. He has not had any hospitalizations related to acute porphyria episodes since the prophylactic therapy. The female patients have received the Normosang therapy for last couple of months with some improvement of symptoms.
Discussion/Conclusion: The porphyrias lead to a deficit of heme synthesis. AIP patients are managed in gastroenterology, hematology, psychiatric, neurology services and management of these patients remains a challenge due to lack of awareness of Hemin therapy. Introduction of outpatient prophylactic Hemin therapy may markedly reduce acute porphyria symptoms and hospital admissions in certain patients.

Friday May 22, 1500–1515

Acylglycine profiling: a new liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, applied to disorders of organic acid, fatty acid and ketone metabolism

Patrick Bherer MS[a,c], Denis Cyr MS[a,c], Daniela Buhas MD[b], Walla Al-Hertani MD[b,c], Bruno Maranda MD[a], Paula J. Waters PhD[a].
[a]Medical Genetics Service, Department of Pediatrics, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, QC. [b]Department of Medical Genetics, McGill University Health Centre, Montreal, QC. [c]Departments of Paediatrics and Medical Genetics, Cumming School of Medicine, University of Calgary, Calgary, AB.

Background: Acylglycine profiles provide information complementary to organic acid and acylcarnitine profiles. A few acylglycines are often included within organic acids methods, but sensitivity and specificity are somewhat limited. Metabolomic studies imply that many acylglycines are present in human urine at low concentrations.
Objectives: We wished to develop an LC-MS/MS method for urine acylglycine profiling in the clinical laboratory; applicable to follow-up testing of "newborn screen positive" cases, investigation of patients with clinical suspicion of inborn errors of metabolism (IEM), and management of patients with confirmed IEM diagnoses.
Methods: Our panel includes 21 acylglycines; some well-established IEM markers plus other molecules considered potentially informative. Butylated acylglycines are gradient separated on a C18 column. MS/MS analysis with multiple reaction monitoring is fully quantitative for 15 acylglycines (linearity 0.01-100 micromol/L) and semi-quantitative for 6 others. Age-related reference ranges were established (282 samples). Validation included > 200 samples from ~ 100 patients with various IEM.
Results: Examples of applications include: 1. Medium-Chain Acyl-coA Dehydrogenase (MCAD) deficiency: Known patients showed a characteristic profile with persistent elevations of hexanoylglycine, suberylglycine, octanoylglycine, heptanoylglycine and phenylpropionylglycine. This method is now integrated into the confirmatory testing algorithm for newborn screening cases in Quebec. 2. Rare disorders, challenging to diagnose: abnormal acylglycine profiles associated with hydroxymethylglutaryl-coA synthase deficiency and glutaric acidemia type 3, among others, will be presented.
Conclusions: We have established a new LC-MS/MS method for urine acylglycine profiling, which is proving valuable in the investigation of various disorders of organic acid, fatty acid and ketone metabolism.
Keywords: Acylglycines; tandem mass spectrometry; organic acidemias; fatty acid oxidation disorders; ketone metabolism

Friday May 22, 1515–1530

The 3' addition of CCA to mitochondrial tRNASer(AGY) is specifically impaired in patients with mutations in the tRNA nucleotidyl transferase TRNT1

Florin Sasarman PhD[a,b], Isabelle Thiffault PhD[b,c], Woranontee Weraarpachai PhD[a], Steven Salomon MSc[a], Catalina Maftei MD[b], Julie Gauthier MD[b], Neil Webb MSc[a,b], Catherine Brunel-Guitton MD[b], Orly Elpeleg MD[d], Grant Mitchell MD[b], Eric A. Shoubridge PhD[a].
[a]Montreal Neurological Institute and Department of Human Genetics, McGill University, Montreal, Canada. [b]Division of Medical Genetics, Department of Pediatrics, CHU Sainte-Justine and Université de Montréal, Montreal, Canada. [c]Center for Pediatric Genomic Medicine, Children's Mercy Hospital, Kansas City, MO, USA. [d]Monique and Jacques Roboh Department of Genetic Research, Hadassah, Hebrew University, Medical Center, Jerusalem, Israel.

Objectives: To characterize the pathogenic mechanism of mutations in TRNT1 encoding the tRNA nucleotidyl transferase enzyme, which catalyzes the addition of the trinucleotide CCA to the 3'end of all transfer RNAs (tRNAs), and functions in both the cytoplasm and mitochondria.
Design and Methods: Exome sequencing revealed TRNT1 mutations in two patients with distinct clinical features. Patient fibroblasts were used to determine the levels of mutant TRNT1 protein, to assess oxidative phosphorylation (OXPHOS) function and to analyze mitochondrial translation and the levels of mitochondrial and cytoplasmic tRNAs before and after overexpression or knockdown of TRNT1.
Results: Patient 1 presented with acute lactic acidosis and developed severe developmental delay, hypotonia, microcephaly, seizures, progressive cortical atrophy, neurosensorial deafness, sideroblastic anemia and renal Fanconi syndrome, dying at 21 months. Patient 2 presented at 3.5 years with gait ataxia, dysarthria, gross motor regression, hypotonia, ptosis, ophthalmoplegia, and abnormal signals in brainstem and dentate nucleus. Muscle from patient 1 showed combined OXPHOS defects, but there was no OXPHOS deficiency in fibroblasts from either patient, despite a tenfold-reduction in TRNT1 protein levels in fibroblasts from patient 1. Furthermore, in normal controls, TRNT1 protein levels are tenfold lower in muscle than in fibroblasts. Complete knockdown of TRNT1 in patient fibroblasts specifically rendered mitochondrial tRNASer(AGY) undetectable and markedly reduced mitochondrial translation, except in polypeptides lacking Ser(AGY) codons.
Conclusions: The clinical phenotype spectrum of TRNT1 mutations is larger than previously thought and appears to be mainly due to impaired mitochondrial translation resulting from defective CCA addition to mitochondrial tRNASer(AGY).

Friday May 22, 1530–1545

NANS deficiency: first discovery of a novel inborn error of metabolism by a combined high throughput metabolic screening & genomics approach

Clara van Karnebeek[a], Maja Tarailo-Graovac[b], Margot Van Allen[c], Tammie Dewan[c], Colin J. Ross[c], Wyeth W. Wasserman[c], Leo Kluijtmans[d], Ron Wevers[d].
[a]BC Children's Hospital. [b]3Centre for Molecular Medicine and Therapeutics. [c]University of British Columbia. [d]Radboud University Medical Centre.

Objectives: A 3 year-old boy presented with epileptic encephalopathy, early developmental arrest, leukodystrophy, dysmorphic features, thrombocytopenia with large platelet forms, skeletal dysplasia and osteoporosis. Metabolic and genetic investigations according to the TIDE protocol were unremarkable. Given his 'lysosomal storage disease phenotype', we enrolled him into the Omics2TreatID program.
Methods: High throughput metabolic screening was performed (Q-TOF-MS analysis) and trio whole exome sequencing analysis (WES) were performed in concert.
Results: Elevated N-acetylmannosamine was identified in the patient's cerebrospinal fluid; this accumulation could be due to a defect in 2 different enzymes. Simultaneously WES identified 16 genes harboring rare, non-synonymous variants. Only 1 gene with compound heterozygous variants was compatible with the metabolomics profile: NANS which encodes N-acetyl neuraminic acid synthase. NMR spectroscopy and Sanger sequencing further confirmed the identity of the elevated metabolite and segregation of NANS variants with disease.
Conclusions: Our neurometabolic disease discovery via simultaneous a metabolomics and genomics approach supports the efficiency of our Omics2TreatID program; the data sets are complementary, and facilitate identification of the candidate gene and potential biomarkers, while simultaneously providing data to support the functional impact of the variants on protein. Currently, validation studies in fibroblasts and using model organisms are ongoing; we are actively searching for other NANS deficiency families. Deficits in sialic acid resulting from NANS deficiency might well prove a therapeutic target via oral supplementation.
Keywords: Inborn Errors of Metabolism (IEM), Intellectual Disability (ID), Genomics, Metabolomics, Discovery, Treatment.
Funding: This work was supported by funding from the B.C. Children's Hospital Foundation as "1st Collaborative Area of Innovation" (www.tidebc.org); Genome BC (SOF-195 grant); Genome BC and Genome Canada grants 174CDE (ABC4DE Project); and the Canadian Institutes of Health Research #301221 grant.

Friday May 22, 1545–1600

FLAGS: candidate gene prioritization scheme based on frequently mutated genes in public exomes

Casper Shyr[a,c,d], Maja Tarailo-Graovac[a,b,c], Michael Gottlieb[a], Jessica JY Lee[a,e], Clara van Karnebeek[c,f,g] and Wyeth W. Wasserman[a,b,c].
[a]Centre for Molecular Medicine and Therapeutics; Child and Family Research Institute, Vancouver BC, Canada. [b]Department of Medical Genetics, University of British Columbia, Vancouver BC, Canada. [c]Treatable Intellectual Disability Endeavour in British Columbia (www.tidebc.org), Vancouver, Canada. [d]Bioinformatics Graduate Program, University of British Columbia, Vancouver BC, Canada. [e]Genome Science and Technology Graduate Program, University of British Columbia, Vancouver BC, Canada. [f]Division of Biochemical Diseases, BC Children's Hospital, Vancouver BC, Canada. [g]Department of Pediatrics, University of British Columbia, Vancouver BC, Canada.

Objectives: Sequencing of exomes of just a few unrelated individuals or family members has revolutionized discovery of pathogenic variants in rare metabolic disorders. As more rare/novel genetic variants continue to be uncovered, there is a major challenge in distinguishing true pathogenic variants from rare benign mutations.
Design and Methods: We used publicly available exome cohorts, together with the dbSNP database, to derive a list of genes (n=100) that most frequently exhibit rare (<1%) non-synonymous/splice-site variants in general populations. We applied the term FLAGS to these frequently mutated genes and analyzed their properties.
Results: Analysis of FLAGS revealed that these genes have significantly longer protein coding sequences, a greater number of paralogs and display less evolutionarily selective pressure than expected. FLAGS are more frequently reported in PubMed literature and more frequently associated with diseased phenotypes compared to the set of human protein-coding genes. We demonstrated an overlap between FLAGS and rare-disease causing genes recently discovered through WES studies (n=10) and the need for replication studies and rigorous statistical and biological analyses when proposing FLAGS as causal for rare disease. Finally, we incorporate FLAGS into a disease-causing exome variant prioritization approach for a family affected by an unknown rare genetic disorder.
Conclusions: We found that the rate at which genes accumulate rare mutations is beneficial information for prioritizing candidates. We provided a ranking system based on the mutation accumulation rates for prioritizing exome-captured human genes, and propose that clinical reports associating any disease/phenotype to FLAGS be evaluated with extra caution.
Keywords: Exome, Genome, Rare Diseases, Metabolic Diseases
Funding: This work was supported by funding from the B.C. Children's Hospital Foundation as "1st Collaborative Area of Innovation" (www.tidebc.org); Genome BC (SOF-195 grant); and the Canadian Institutes of Health Research #301221 grant.

Saturday May 23, 1000–1015

GeneYenta: A phenotype-based rare disease case matching tool based on online dating algorithms for the acceleration of exome interpretation

Michael M. Gottlieb[a], David J. Arenillas[b], Savanie Maithripala[c], Zachary D. Maurer[d], Maja Tarailo-Graovac[b], Linlea Armstrong[c], Millan Patel[c], Clara van Karnebeek[c], and Wyeth W Wasserman[b,c].
[a]Graduate Program in Bioinformatics, University of British Columbia, Vancouver, British Columbia, Canada. [b]Department of Medical Genetics,Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia, Vancouver, British Columbia, Canada. [c]Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada. [d]Stanford University, Stanford, California.

The advent of next-generation sequencing technologies has facilitated the detection of causal variants of genetic diseases. In order to establish causality, it is often necessary to compare the genomes of unrelated individuals with the same phenotype. Such matches may be difficult to find if the disease is rare. We present a web tool, GeneYenta, which facilitates patient phenotype matching and allows clinicians to coordinate detailed comparisons for cases with similar phenotype. The system is focused on phenotype annotation and explicitly limits the use of confidential information to reduce the threshold for participation. The matching procedure is inspired by online dating services and uses an ontology-based semantic case matching algorithm with clinician attribute weighting. We compare the efficacy of our matching algorithm with three other matching algorithms and find that inclusion of clinician weights can improve phenotype matching.
Keywords: rare genetic disorders; phenotype annotation; case matching; human phenotype ontology

Saturday May 23, 1015–1030

OMICS2TREATID: A collaborative approach to accelerate the discovery of rare neuro-metabolic diseases

Maja Tarailo-Graovac[a,b,c], Gabriella Horvath[c,d,e], Ramona Salvarinova[c,d,e], Casper Shyra[c,f], Cynthia Ye[a,b,c], Leo Kluijtmans[g], Ron A. Wevers[g], Sandra Sirrs[h], Hilary Vallance[i], Sylvia Stockler-Ipsiroglu[c,d,e], Graham Sinclair[i], Colin J. Ross[b,e], Wyeth W. Wasserman[a,b,c], Clara D. van Karnebeek[a,c,d,e]. [a]Centre for Molecular Medicine and Therapeutics, Vancouver, Canada. [b]Department of Medical Genetics, University of British Columbia, Vancouver, Canada. [c]Treatable Intellectual Disability Endeavour in British Columbia (www.tidebc.org), Vancouver, Canada. [d]Division of Biochemical Diseases, BC Children's Hospital, Vancouver, Canada. [e]Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada. [f]Bioinformatics Graduate Program, University of British Columbia, Vancouver BC, Canada. [g]Radboud University Medical Centre, Nijmegen, Netherlands. [h]Department of Internal Medicine, University of British Columbia, Vancouver, Canada. [i]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada.

Objectives: Intellectual disability (ID) affects 2.5% of the population worldwide, and with its co-morbidity poses a significant emotional and health-economic burden. Establishing accurate and timely diagnosis is hindered by etiologic heterogeneity and the large number of genes yet to be discovered. Inborn errors of metabolism (IEMs) constitute the largest group of rare genetic diseases amenable to targeted treatments (n>90, identified by our TIDE group). In our Omics2TreatID program, we combine the exquisite metabolic phenotyping with whole exome sequencing (WES) to accelerate discovery, with focus on potentially treatable neuro-metabolic diseases.

Design and Methods: WES analysis was completed in 55 ID patients (from 45 families) with unexplained neuro-metabolic phenotypes. The patients were predominantly from non-consanguineous European Caucasian families with a single affected child. Patients were extensively phenotyped according to the TIDE protocol, along with chromosome micro-array and single gene tests, enriching our cohort for novel disorders.

Results: We established a diagnosis in 89% of the families. We identified mutations in 46 different genes: 16 novel genes (35%), 24 known genes (52%) with novel phenotypes and 6 (13%) with known phenotypes. Importantly, 5 novel neuro-metabolic diseases potentially amenable to treatment were discovered, while in another 11 families the genetic diagnosis significantly impacted management.

Conclusions: Our diagnostic yield of 89% emphasized strength of our collaborative, semi-automated gene discovery WES-based approach. Furthermore, utilizing a metabolic phenotype not only facilitates diagnosis and gene discovery with subsequent validation, but also enriches for a subset of ID conditions amenable to treatment, thereby impacting clinical practice and patient outcomes.

Keywords: Inborn Errors of Metabolism (IEM), Intellectual Disability (ID), Bioinformatics semi-automated pipeline, Discovery, Treatment

Funding: This work was supported by funding from the B.C. Children's Hospital Foundation as "1st Collaborative Area of Innovation" (www.tidebc.org); Genome BC (SOF-195 grant); Genome BC and Genome Canada grants 174CDE (ABC4DE Project); and the Canadian Institutes of Health Research #301221 grant

Saturday May 23, 1130–1145

The metabolic diet app suite: medical diets made easier using digital technologies

Gloria Ho BSc[a], Keiko Ueda RD, MPH[a]. Roderick Houben[c], Jeff Joa[c], Barbara Cheng RD[a], Alette Giezen RD[a], Clara Van Karnebeek MD, PhD[a,b]. [a]Division of Biochemical Disease / TIDE-BC, Department of Pediatrics, B.C. Children's Hospital, Vancouver, B.C. [b]Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, B.C. [c]Health2Media, Vancouver, B.C.

Background & Objectives: Inborn errors of metabolism (IEM) diet therapies are known to be burdensome, with lack of food nutrient information often leading to noncompliance and frustration for patients and families. Digital technologies provide the opportunity to develop Metabolic Diet Applications (MDApps), which can help families overcome these problems. We aimed to develop secure digital Applications comprising nutrient information with options for tracking and exporting food records, to facilitate therapeutic compliance for IEM patients on diets.

Design and Methods: Nutrient information is supplied by the Genetic Metabolic Dietitians International (GMDI) MetabolicPro™ database. Metabolic physicians, registered dietitians and families tested the app. Feedback was submitted through an online survey as well as through the Application feedback function.

Results: The MDApps are free, user-friendly, online apps available on 2 platforms (computer and mobile device) via www.mdapp.org. The MDApps are tailored to more than 15 individual IEMs. Each App provides specific nutrient information on over 100,000 different food products. Functions on the MDApps include: disease specific nutrient counting, adding foods and recipes, and sharing food diary records with their clinic. Brief introductions and App use instructions are provided for IEMs, along with links to reliable online resources.

Conclusions: The MDApp suite enhances personalized treatment of IEMs via digital medicine. Apps are popular digital tools; use of MDApps will promote better patient understanding and control of their disease. Change in adherence will be evaluated. The MDApp is a tool, and therefore not intended to be a replacement for medical-metabolic nutritional professional advice.

Keywords: digital tools, treatment, adherence, metabolic diets

Funding: BC Children's Hospital Foundation (1st Collaborative Area of Innovation' grant) & Rare Diseases Foundation Microgrant

Saturday May 23, 1145–1200

N-of 1 study with oral S-adenosyl methionine as adjunct to L-arginine, glycine and creatine supplements for treatment of creatine transporter (SLC6A8) deficiency

Sravan Jaggumantri[a,f], Mary Dunbar[b], Vanessa Edgar, Christina Mignone[c], Theresa Newlove[d], Rajavel Elango[e,f], Jean-Paul Collet[e,f], Michael Sargeant[c], Sylvia Stockler[a,e,f], Clara D.M. van Karnebeek[a,e,f]. [a]Division of Biochemical Diseases (TIDE-BC), Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, Canada. [b]Division of Pediatric Neurology, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, Canada. [c]Department of Radiology, BC Children's Hospital, University of British Columbia, Vancouver, Canada. [d]Department of Psychology, BC Children's Hospital, University of British Columbia, Vancouver, Canada. [e]Department of Pediatrics, University of British Columbia, Vancouver, Canada. [f]Child and Family Research Institute, University of British Columbia, Vancouver, Canada.

Objectives: To evaluate the safety and efficacy of oral S-adenosyl methionine (SAMe) as adjunct treatment of creatine transporter deficiency (CTD).

Methods: We conducted an open label n-of-1 study in 2 patients with confirmed CTD diagnosis, already treated with oral creatine, glycine, arginine. SAMe was given orally at a dose of 50mg/kg/day (TID) for12 months. Outcomes: cerebral creatine with proton magnetic resonance spectroscopy, Seizure activity with seizure log book and electroencephalogram, muscle mass with Bioelectrical Impedence Analyzer; Neurodevelopmental outcome using standardized psychometric scales; and a priori treatment expectations using in-house patient reported outcome technique (POSI).

Results: Significant and reproducible issues with sleep and behaviour were noted in both patients on a dose of 50/mg/kg/day. Patient #1 was treated with SAMe for a period of 12 months. Patient#1 did not show increase in intra-cerebral creatine; however significant improvement in speech/language, communication, muscle mass were observed as well as in two of three POSI. Patient #2 withdrew from the study after being treated with SAMe for 1 month and did not come for any follow up. However the mother reported improvement in speech over email at the time of treatment.

Conclusions: SAMe has potential adverse effects at higher dosages. At a dosages of 20mg/kg/day, it was safe and tolerated in patient #1, with the potential to further improve muscle mass and speech/communication. More research is needed to replicate these findings in larger number of patients, to further delineate the optimal and safe dosage. The importance of personalized outcomes and parent/patient involvement is highlighted.

Keywords: personalized outcomes, new treatments, SLC6A8 Deficiency, S-Adenosyl Methionine

Saturday May 23, 1200–1215

Sapropterin-responsiveness testing in PKU patients: the Calgary Metabolic Clinic approach

Rebecca L. Sparkes M.D.[a,b,c], Catherine M. Rombough R.D.[a,c], Melanie J. Reeves R.D.[a,c], Karin E. Klassen R.N.[a,c], Ashley L. Marsh M.A., R.Psyc.[c]. [a]Inherited Metabolic Disorders Clinic, Alberta Children's Hospital, Calgary, AB. [b]Department of Medical Genetics, Cumming School of Medicine, University of Calgary, Calgary, AB. [c]Alberta Health Services.

Objectives: To implement a robust program for determining sapropterin-responsiveness in adults and children with phenylalanine hydroxylase (PAH) deficiency/phenylketonuria (PKU).

Design and Methods: Southern Alberta patients/families with PAH deficiency/PKU requiring dietary restriction of phenylalanine (Phe) to maintain blood Phe levels between 120 and 360 micromol/L were invited to be tested for sapropterin-responsiveness. Interested patients completed a four week baseline assessment, followed by a four week trial of sapropterin dihydrochloride 20 mg/kg/day; both phases involved weekly blood Phe levels, biweekly diet records, and a validated, age-appropriate, neuropsychological/behavioral questionnaire. Results were reviewed by a metabolic physician, dietitian and clinical psychologist to determine each patient's responsiveness.

Results: Of 46 PKU patients/families invited, 36 attended an information session. Twelve patients (eight females and four males, age range two years to 37 years) have completed testing. Eight were deemed non-responsive and discontinued sapropterin. Four patients with classical or mild PKU were deemed responsive based on a significant decrease in Phe levels and/or improved Phe tolerance. Two of the responders are now able to maintain target blood Phe levels while consuming unrestricted diets; the other two have liberalized their diets but continue to require some protein restriction and Phe-free formula. Improvement of the neuropsychological profile on treatment was observed only in biochemical responders.

Conclusions: Using a consistent, objective approach, one-third of PKU patients tested had a robust biochemical, clinically significant response to sapropterin. The absence of established reimbursement criteria remains a barrier to ongoing treatment in responsive individuals in Alberta who do not have private insurance coverage.

Keywords: PKU, PAH deficiency, sapropterin, Kuvan®, responsiveness

Funding: An educational grant from BioMarin Pharmaceutical Inc. supported the material costs and additional administrative, dietitian and psychologist time required to implement the testing program.

P101 Improving the collection of cerebrospinal fluid neurotransmitters: a resident initiative

Mary J. Dunbar MD, MSc.
Division of Pediatric Neurology, Department of Pediatrics, BC Children's Hospital, University of British Columbia, Vancouver, Canada.

Objectives: Cerebrospinal fluid (CSF) is collected by lumbar puncture for neurotransmitter testing at BC Children's Hospital approximately 80 times per year. It was very technically challenging due to the difficulty holding the five special tubes. The objective of this project was to design a superior collection method to improve the ease, safety and effectiveness of CSF neurotransmitter collection.

Design and Methods: A tube holder was designed to hold the five collection tubes and was produced by a plastics company. CSF neurotransmitter tube holders were distributed to the residents. An anonymous survey was performed at the time of holder dissemination in July 2014, followed by a second survey six months later. Qualitative data was also collected.

Results: The senior pediatric residents and fellow were surveyed anonymously. Prior to the intervention, the assistant was holding all five tubes only 13% of the time. No resident had a >90% success rate, defined as not missing any drops of CSF. The majority of residents had a success rate of <50%. The procedure was not standardized. After the device was used for six months, all but one resident had a >90% success rate and the majority of residents performed the procedure in a standardized fashion.

Conclusions: The identification of a substandard procedure method inspired a simple device that has standardized this common procedure and improved the safety and quality of the data. This has been embraced by the neurology, pediatric and metabolic groups and adopted as the new standard of care.

Keywords: Neurotransmitter, Lumbar Puncture, Invention, Cerebrospinal Fluid

P102 Treatable inborn errors of metabolism presenting as cerebral palsy mimics: systematic literature review

Emma L. Leach[a,b], Michael Shevell[c,d], Kristin Bowden[b], Sylvia Stockler-Ipsiroglu[b,e,f], Clara D.M. van Karnebeek[b,e,f,g].
[a]Provincial Medical Genetics Program, BC Women's Hospital, Vancouver, Canada. [b]University of British Columbia, Vancouver, Canada. [c]Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada. [d]Department of Neurology/Neurosurgery, Montreal Children's Hospital, McGill University, Montreal, Canada. [e]Division of Biochemical Diseases, Department of Pediatrics, BC Children's Hospital, Vancouver, Canada. [f]Treatable Intellectual Disability Endeavour in British Columbia, Vancouver, Canada. [g]Centre for Molecular Medicine and Therapeutics; Child and Family Research Institute, Vancouver, Canada.

Objectives: Inborn errors of metabolism (IEMs) have been anecdotally reported in the literature as presenting with features of cerebral palsy (CP) or misdiagnosed as 'atypical CP'. A significant proportion is amenable to treatment, showing improvement of symptoms or with the potential to halt disease progression and prevent further damage.

Design and Methods: We performed a systematic literature review to identify all reports of IEMs presenting with CP-like symptoms before 5 years of age, and selected those for which evidence for effective treatment exists.

Results: We identified 54 treatable IEMs reported to mimic CP, across 13 different biochemical categories. A further 13 treatable IEMs were included, which can present with CP-like symptoms according to expert opinion, but for which no reports in the literature were identified. For 26 of these IEMs, a treatment is available that targets the primary underlying pathophysiology, and for the remainder (n=41), treatment exerts stabilizing/preventative effects. Thirty-eight (57%) of the treatable IEMs mimicking CP can be identified by ready available metabolic screening tests in blood or urine, while the remaining IEMs require more specific and sometimes invasive tests.

Conclusions: (1) A surprisingly large number of IEMs can present with CP symptoms, as 'CP mimics', (2) although individually rare, a large proportion of these diseases are treatable such that neurological damage can be reversed or prevented, (3) clinician awareness of treatable CP mimics is important for appropriate screening, diagnosis, and early intervention, and (4) systematic studies are required to elucidate the collective frequency of treatable IEMs in CP.

Keywords: Inherited metabolic diseases, Therapy, Diagnosis, Atypical cerebral palsy, Movement disorders
Funding: This work was performed as part of the Treatable Intellectual Disability Endeavour in British Columbia (TIDE-BC, www.tidebc.org) funded by BC Children's Hospital as a Collaborative Area of Innovation.

P103 Niemann-Pick type C (NPC): Canadian Management Guidelines

Serge Melançon[a,b], Joe T.R. Clarke[c], Sandra Sirrs[d], Chitra Prasad[e], Margaret Mackrell[c], Bruno Maranda[f], Mary Anne Patterson[g], Valerie Poullos[g], Julian Raiman[c], Sylvia Stockler-Ipsiroglu[h], Aneal Khan[i], Oksana Suchowersky[j].
[a]McGill University Health Centre. [b]Montreal Children's Hospital. [c]Hospital for SickKids. [d]Vancouver General Hospital. [e]Western University/LHSC London. [f]CHU Sherbrooke. [g]Mount Sinai Hospital. [h]BC Children's Hospital. [i]University of Calgary/Alberta Children's Hospital. [j]University of Alberta Hospitals.

Niemann-Pick disease type C (NPC) is a rare but fatal disorder with an incidence of 0.82 cases per 100, 000 live births. The disease is pan-ethnic, with 95% of all disease due to mutations in the NPC1 gene and 5% in the NPC2 gene. It can manifest at any age with severe neurodegenerative symptoms, visceromegaly, and cholestasis, and in adults can present with psychosis, dementia and no organomegaly. The diagnosis of NPC can be challenging due to non-specific symptoms and the limited availability of diagnostic tests. There is no cure for NPC, treatment is supportive, aimed at symptom control and comfort, as the degenerative symptoms progress. These guidelines cover the clinical features, diagnosis, treatment and the evidence for using miglustat in patients with NPC in Canada. The guidelines are compared to the United Kingdom National Commissioning Group (2009) and the European Working Group guidelines (2009) for NPC.

P104 CACNA1A mutation in a 5 year old boy with recurrent episodes of encephalopathy

Lesley A. Turner MD[a], David Buckley MD[b], Gena Shepherd MSc[a], Marisa Chard MD[b].
[a]Department of Medical Genetics, Eastern Health, St. John's, Newfoundland and Labrador. [b]Department of Pediatrics, Eastern Health, St. John's, Newfoundland and Labrador.

CACNA1A mutations are associated with three autosomal dominant conditions; familial hemiplegic migraine type 1 (FHM1), episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6). These conditions can have overlapping features including episodic ataxia and nystagmus. Very recently it has been recognized that a minority of patients with mutations in the CACNA1A gene can have epilepsy, encephalopathic episodes and learning difficulties.

We present a five year old boy with recurrent encephalopathic episodes. Prior to the episodes the boy was described as being unusually active and energetic for one to two days. He would then become unsteady on his feet and ultimately become very weak and unresponsive. The family live in a remote community and when the episodes occurred the boy was transferred to the local hospital for further investigations. Metabolic testing including urine organic acids, ammonia, lactate, glucose and plasma amino acids was normal. However, often these investigations were not done in the acute setting. EEG on several occasions showed diffuse slowing of an encephalopathic type. Fibroblast analysis for pyruvate dehydrogenase activity was normal. Given the ataxia proceeding the episodes, molecular testing for ATP1A2, ATP1A3, and CACNA1A was requested and revealed a likely pathogenic mutation in the CACNA1A gene. This case presentation as well as recent published literature suggests that mutations in the CACNA1A gene should be considered in cases of recurrent childhood encephalopathy, particularly with normal metabolic screening.

P105 Mutations in ACC2 encoding mitochondrial acetyl-coA carboxylase 2 in a child with biotin-responsive multiple carboxylase deficiency

Gabriella A. Horvath[a,e], Lin-Hua Zhang[a,e], Patricie Burda[f], Graham Sinclair[b,e], Casper Shyr[d,e], Amit P. Bhavsar[c,e], Wyeth W. Wasserman[c,d,e], Colin J. Ross[a,c,e], Matthias R. Baumgartner[f], Clara D. van Karnebeek[a,d,e]. [a]Department of Pediatrics, University of British Columbia, Vancouver, BC. [b]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC. [c]Department of Medical Genetics, University of British Columbia, Vancouver, BC. [d]Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, Vancouver, BC. [e]Treatable Intellectual Disability Endeavour in British Columbia, Vancouver, BC. [f]Division of Metabolism and Children's Research Center, University Children's Hospital, CH-8032, Zurich, Switzerland.

Background: The Omics2TreatID study aims to identify novel inborn errors of metabolism. We investigated a 4 year-old child with speech delay and recurrent fever-induced episodes of lethargy, lactic acidosis and metabolites suggestive of multiple carboxylase deficiency, responsive to biotin.

Design and Methods: Trio whole-exome sequencing, followed by Sanger confirmation of candidate variants was performed. Functional analyses of the variants were performed in immortalized skin fibroblast expression systems.

Results: Compound heterozygous mutations c.1709A>G (p.Tyr570Cys) and c.2503A>G, (p.Met835Val) in ACC2 encoding acetyl-coA carboxylase 2 were considered the strongest candidate. Enzymatic activity of mutants Y570C, M835V and combination, in transfected fibroblasts was 58%, 31% and 40% of wildtype ACC2. ACC2 activity in patient fibroblasts decreased by ~18% when incubated at 40oC, reflecting the metabolic episodes triggered by fever in the patient. The ACC2 activity of patient fibroblasts increased with exposure to biotin, indicating normal biotin responsiveness. The amount of biotin-bound ACC2 protein from patient cells decreased ~60% by biotin-pull down and immunoblotting assay.

Discussion: Our data support the damaging effect on protein function of the patient's ACC2 mutations. To explain the causal relation with the multiple-carboxylase deficiency phenotype, we postulate that since malonyl-CoA, generated by ACC2 in mitochondria, is a key regulator for fatty acid β oxidation and energy homeostasis, the deficient ACC2 activity alters the physiological conditions in mitochondria. Further experiments as well as identification of other similar families are required to further validate ACC2 deficiency as a novel inborn error of metabolism presenting with biotin responsive metabolic crises.

Keywords: treatment, discovery, multiple carboxylase deficiency, biotin, metabolic crisis

Funding: BC Children's Hospital Foundation, Canadian Institutes of Health Research, Genome BC

P106 No patient access to first drug for PKU. Are public drug programs ignoring the Common Drug Review?

John Adams.

Canadian PKU and Allied Disorders.

Case study of policy inconsistencies between the Common Drug Review (CDR) and most government drug plans, lack of rationale for patient access criteria for the two programs acting consistently with CDR report and off-label uses of the drug without a CDR recommendation.

No patient has been able to access the only drug to treat PKU (phenylketonuria) through a CDR program. Seven provinces have not acted on a note which qualified a Do Not List recommendation. Two listed the drug for managed access; no patient has been approved and treating doctors and patients are critical of access criteria for not being evidence based.

PKU is a rare, genetic, metabolic disorder threatening brain functions of affected persons; that threat comes from everything a patient consumes containing protein. Provinces test newborns to find the 1:12,000. PKU is treated by protein restriction and synthetic substitution.

Health Canada approved Kuvan for PKU in 2010. CDR recommended Do Not List in January 2011, adding a Note saying it would be worthwhile for the manufacturer to work with the plans to decide what health improvements should occur in patients that would warrant paying for Kuvan.

ON and SK negotiated a listing; physicians have criticized access criteria as lacking clinical sense and developed without consultation.

Plans pay for Kuvan for two off-label uses: treatment of biopterin deficiency, originally called malignant PKU, and differential diagnosis.

One provincial disability program has approved the drug for two patients.

Quebec listed for PKU women pregnant or considering a pregnancy and approved other patients under individual, exceptional access.

Policy inconsistencies make it difficult to sustain public confidence and trust in public drug plan decisions.

P107 Adenosine deaminase deficiency; new patients identified through newborn screening

Osama Y. Al-Dirbashi[a,b,c], Dennis E. Bulman[a,b,c], Pranesh Chakraborty[a,b,c]. [a]Newborn Screening Ontario, Children's Hospital of Eastern Ontario. [b]Children's Hospital of Eastern Ontario Research Institute. [c]Department of Pediatrics, University of Ottawa, Ottawa, Ontario.

Neonatal Screening of Severe Combined Immunodeficiency (SCID) aims at early detection of affected newborns. SCID is a genetically heterogeneous disorder that can be caused by defects in a number of genes. Determination of the etiology of SCID is important as this information may guide implementing the most effective management plan. Mutations in the ADA gene encoding Adenosine Deaminase (ADA) result in reduced enzyme activity. This enzyme is involved in the purine salvage pathway which deaminates Adenosine and Deoxyadenosine into Inosine and Deoxyinosine, respectively. When ADA activity is missing, the immune system becomes compromised due to the cytotoxic effects of accumulating ADA substrates on various lymphocyte subtypes. This cytotoxicity leads to T-cell, B-cell and natural killer cell lymphopenia. It is known that ADA-SCID accounts for 20% of all SCID cases worldwide. In our lab, dried blood spot (DBS) samples are screened for SCID by measuring T-cell receptor excision circles (TREC). DBS samples with low TREC count are analyzed for purine profiling by an in-house developed tandem mass spectrometric method. This method detects Adenosine, Deoxadenosine, Guanosine, Deoxyguanosine, Inosine, Deoxyinosine, Xanthine and Hypoxanthine simultaneously. Since we started screening for SCID in August 12, 2013, more than 205,000 babies were screened. Among these 4 ADA-SCID positives have been reported, with no false positive or negative cases identified.

The addition of the purine profiling assay to complement TREC analysis has improved screening for ADA-SCID by introducing an etiologic focus. In Ontario, ADA-SCID is occurring at a frequency of approximately 1 in 50,000.

P108 Adult patients with phenylketonuria do not have high rates of hypercalciuria

Caroline E. Selvage BSN RN[a], Jennifer S. Branov BSc RD[a], Taryn M. Bosdet BSc RD[a], Sarah A. Rosen BSc RD[a], Sandra M. Sirrs MD FRCPC[a,b]. [a]Adult Metabolic Diseases Clinic, Vancouver General Hospital, Vancouver, BC. [b]Clinical Associate Professor, Division of Endocrinology, University of British Columbia.

Objective: Recent data suggest that patients with PKU using medical foods may have hypercalciuria. Our objective was to define the prevalence of hypercalciuria in the adult patient with PKU.

Design: All adults with PKU at our centre were asked to have random urine samples at the time of scheduled annual bloodwork (which includes data on renal function and serum calcium (sCa)) to evaluate the ratio of urine calcium to creatinine (UCa/Cr). Patients with elevated UCa/Cr were asked to do a 24 hour urine collection for calcium.

Results: In a 12 month period, 48 patients (25 males and 23 females; mean age 34 years; age range 18-74 years) had blood and urine samples. All patients were prescribed medical foods although compliance was variable. The mean eGFR was 102.5 ml/min with a range of 53-124 ml/min. Only one patient had an eGFR <60. The mean sCa was 2.31 mmol/L and all sCa results were in the normal range. The range of UCa/Cr was 0.006 to 0.91 mmol/mmol, with a mean of 0.29mmol/mmol (normal <0.4 mmol/mmol). Six patients had UCa/Cr above the normal range. Of these 6 patients, 4 went on to complete 24 hr urine collections for calcium which 3 were normal, 1 declined to do a 24 hr collection and 1 was unable to complete a 24 hr urine collection due to urinary incontinence. One patient had modest hypercalciuria

(7.8 mmol/d; normal <6.4 mmol/day) with normal renal function, serum calcium, PTH and 25-OHD levels.
Conclusion: Hypercalciuria was not common in our treated adult PKU cohort.

P109 24-Month Results from the Eliglustat ENCORE Phase 3 Trial of Eliglustat versus Imiglucerase in Adults with Gaucher Disease Type 1 Stabilized on Enzyme Therapy
Thomas Andrew Burrow[a], Timothy M. Cox[b], Guillermo Drelichman[c], Renata Cravo[d], Manisha Balwani[e], Ana Maria Martins[f], Elena Lukina[g], Barry Rosenbloom[h], Leorah Ross[i], Jennifer Angell[i], Judith M Peterschmitt[j] .
[a]Cincinnati Children's Hospital Medical Center. [b]University of Cambridge, Addenbrooke's Hospital, Cambridge, UK. [c]Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina. [d]HEMORIO, Rio de Janeiro, RJ, Brasil. [e]Mt. Sinai Hospital. [f]Universidade Federal de São Paulo, São Paulo, SP, Brasil. [g]Hematology Research Center, Moscow, Russia. [h]Cedars-Sinai/Tower Hematology Oncology, Beverly Hills, CA, USA. [i]Genzyme, a Sanofi Company. [j]GE.
Introduction: Eliglustat is a novel oral substrate reduction therapy approved in the United States, Europe, and Australia for Gaucher disease type 1. This open-label, non-inferiority Phase-3 trial (ENCORE, NCT00943111, Genzyme, a Sanofi company) evaluated eliglustat and imiglucerase in patients who had reached pre-specified therapeutic goals after ≥3 years of enzyme therapy. We report efficacy data from the 12-month primary analysis period and the first 12 months of the extension period in which all patients received eliglustat.
Methods: Patients were randomized 2:1 eliglustat: imiglucerase. The primary efficacy endpoint was percent of patients remaining stable on a composite of spleen, liver, hemoglobin, and platelet parameters. As this was a non-inferiority trial, efficacy analyses were performed on the per-protocol population (99 eliglustat, 47 imiglucerase patients).
Results: Eliglustat was non-inferior to imiglucerase; after 12 months, 85% of eliglustat and 94% of imiglucerase patients met the primary endpoint, maintaining all four goals (lower bound of 95% CI of difference [-17.6%] within pre-specified [-25%] non-inferiority margin). 145/159 patients (91%) completed 24 months of treatment. In the 12-month extension, clinical stability by both composite and individual measures (spleen, liver, hemoglobin, and platelets) was maintained by >85% of patients — those who remained on eliglustat for 24 months and those who switched from imiglucerase to eliglustat. Most adverse events were mild or moderate in severity. A patient survey at baseline and 12 months showed >90% preference for oral treatment.
Conclusions: In the ENCORE study, patients maintained hematologic and organ volume stability while on eliglustat for 12 or 24 months.

P110 GOT2 as a novel cause of serine deficiency syndrome
Ian A. Garber[a], Clara van Karnebeek[b].
[a]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC. [b]Department of Pediatrics, University of British Columbia, Vancouver, BC.
Objective: A 5-year-old boy presented with early-onset global developmental delay, acquired microcephaly, and severe seizure disorder refractory to anti-epileptic treatment. Biochemical testing revealed high lactate and low serine levels in blood and cerebrospinal fluid. Within three months of beginning serine supplementation, there was dramatic clinical improvement. Further improvement was noted with addition of vitamin B6. Molecular analysis of the three known serine deficiency syndrome genes (3-PGDH, PSAT, and PSP) was negative, therefore the patient was enrolled in our Omics2TreatID program.
Design and Methods: Trio whole exome sequencing (WES) was performed with a custom bioinformatics pipeline.
Results: Out of 16 candidate genes identified, only GOT2 was found to have a biochemical relationship to the serine deficiency phenotype. GOT2 is the mitochondrial isoform of aspartate aminotransferase, and catalyzes the conversion of aspartate to glutamate, which in turn is required as an amino donor in the second-to-last step of serine biosynthesis. GOT2 also plays a crucial role in the malate-aspartate shuttle, providing a connection to elevated lactate. Response to vitamin B6 may be explained by pyridoxine's role as a cofactor for GOT2.
Conclusions: GOT2 deficiency represents an entirely novel mechanism for serine deficiency. Given the intersection with other important pathways such as the malate-aspartate shuttle and neurotransmitter synthesis, it is expected to have more far-reaching consequences than the three known forms of serine deficiency. Functional and model organism studies are underway; we aim to identify other serine deficiency families with GOT2 variants.
Keywords: Neurometabolic disease, Seizure disorder, Whole exome sequencing, Novel genetic variant

P111 Phenylketonuria treated with sapropterin (Kuvan) in pregnancy: The first reported case in Canada
Alana M. Newman MD[c], , Maggie A. Chapman BSc PDt[a], Michelle Steeves-Wall BScN RN[a], Andrea MacLean BScN RN[a], L. Jane Gillis MSc MD[a,b].
[a]Maritime Medical Genetics Service, IWK Health Centre, Halifax NS. [b]Dalhousie University, Halifax NS. [c]Memorial University of Newfoundland, St. John's NL.
Objective: We present an 18 year old healthy primigravida with atypical phenylketonuria (PKU). She is heterozygous (R408W/R68S). The R68S mutation has been associated with tetrahydrobiopterin responsiveness, and she had been treated with sapropterin (Kuvan®), prior to conception and during pregnancy as her Phe levels could exceed 1200 mmol/L. Our objective is to describe the management and outcomes of the first reported pregnancy in Canada treated with sapropterin.
Design and Methods: The patient was followed closely during her pregnancy starting at 5 weeks 6 days gestation. Data collection included blood phenylalanine (Phe) levels, routine bloodwork for pregnancy monitoring, ultrasound results, sapropterin dose, diet records, and details of her clinical course.
Results: The patient was continued on sapropterin throughout pregnancy, at her regular dose of 20 mg/kg/day; this required one dose adjustment at approximately 32 weeks gestation due to pregnancy weight gain. She maintained acceptable blood phenylalanine (Phe) levels with the majority (74%) falling into our recommended pregnancy management range of 120-240 mmol/L. Aside from nausea, there were no complications throughout pregnancy. She had an uncomplicated delivery at term. The infant had a normal physical examination and to date is developing normally.
Conclusions: This is the first reported case in Canada in which a patient was treated with sapropterin prior to conception and throughout pregnancy. Along with case reports in the literature, the favourable outcome in this case supports the safety and efficacy of sapropterin during pregnancy, in assisting the maintenance of acceptable Phe levels throughout pregnancy.
Keywords: Phenylketonuria, sapropterin, pregnancy

P112 Short-term storage of intact skeletal muscle for measurement of mitochondrial function by HRR identifies varied alteration to the complexes of the electron transport chain
Lauren MacNeil[a], Jenna Gillen[a], Martin Gibala[a], Murray Potter[a], Mark Tarnopolsky[a].
[a]McMaster University.
Measurement of electron transport chain function provides important information for diagnosing inborn mitochondrial myopathies. Although traditionally used for scientific inquiry, the small amount of tissue required for high resolution respirometry (HRR) on intact, permeabilised skeletal muscle fibres makes it favorable as a clinical assay. However, work is needed to quantify alterations to enzyme function that result from time spent ex vivo in the unfrozen state.
Objective: To determine the impairment in activity of complexes involved in electron transfer (I – IV) in intact tissue stored at 4°C.
Design and Methods: Muscle tissue was collected from the vastus lateralis of 17 healthy men and immediately placed in ice-cold relaxing buffer. A portion was immediately permeabilized with saponin and measured by HRR. Remaining tissue was left refrigerated in buffer until permeabilization and measurement after one or more of the following storage times: 24 h, 48 h, 72 h and 7 d. All measurements were normalized to wet tissue weight.
Results: Complex I activity was the first and most affected by time, falling by 45% in 24 h ($p = 0.04$) and reaching almost complete loss of function at 7 d (-83%, $p = 0.008$). Complexes II and III were not significantly impaired until 7 d, when they were 44% ($p = 0.03$) and 50% ($p = 0.02$) lower respectively. Complex IV was unaltered at any time point.

Conclusion: These results indicate that immediate measurement following excision is imperative when using HRR to quantify mitochondrial function, particularly with regards to CI activity.
Keywords: skeletal muscle, mitochondrial respiration, stability
Funding: This research was funded in part by MitoCanada and NSERC.

P113 Rhabdomyolysis due to LPIN1 deficiency, the first case of maternal isodisomy – literature review and new therapeutic avenues
Inge A. Meijer MD, PhD[a], Florin Sasarman PhD[b], Catalina Maftei MD[b], Michel Vanasse MD[a], Philippe Major MD[a], Virginie Poisson GC[b], Elsa Rossignol MSc, MD[a], Grant A Mitchell MD[b], Catherine Brunel-Guitton MD[b].
[a]Division of Pediatric Neurology, Department of Pediatrics, CHU Sainte-Justine, Université de Montréal, Montreal, Canada. [b]Division of Medical Genetics, Department of Pediatrics, CHU Sainte-Justine, Université de Montréal, Montreal, Canada.
Objectives: *LPIN1* deficiency is a common cause of childhood rhabdomyolysis. We report a patient who expands the clinical and genetic spectra of *LPIN1* deficiency and review previous reports.
Case Report: This 6-year-old boy presented with myalgia and rhabdomyolysis at age four years. He has had five episodes (CK levels up to 300 000 U/L). He has persistent interictal myalgia and CK elevations. The patient is homozygous for a novel frameshift mutation, c.1381delC (p.Leu461SerfsTer47), in *LPIN1*. Family analysis reveals maternal isodisomy as the underlying genetic mechanism.
Results: We identified 35 additional cases of *LPIN1* deficiency and 19 reported causal *LPIN1* mutations, with no clear genotype-phenotype correlation. Patients typically presented before the age of six years with rhabdomyolysis triggered by infection, fever, exercise or fasting. The main complications are acute renal failure, electrolyte disturbances and cardiac dysfunction. Mortality is 30%, with patients dying during rhabdomyolysis crisis. Standard crisis management involves aggressive hydration to avoid renal failure, close monitoring of electrolyte levels and of cardiac function and adequate caloric intake. During 2 crises the patient briefly received dexamethasone, 0.6 mg/kg/24h. CK remained <12000 U/L, i.e. less than usual during his crises.
Conclusions: The patient demonstrates previously-unreported features of *LPIN1* deficiency: maternal isodisomy, c.1381delC homozygosity and interictal CK elevation. The high risk of mortality during rhabdomyolysis stresses the importance of prompt management, close monitoring and the need for better treatments. We speculate that brief treatment with dexamethasone, which suppresses inflammation and upregulates lipin-1 expression, may be beneficial during rhabdomyolytic crises.
Keywords: *LPIN1*, rhabdomyolysis, isodisomy, treatment, dexamethasone

P114 Is Glycine N-Methyl transferase (GNMT) deficiency underdiagnosed?
Bojana Rakić[a], Graham Sinclair[a], Sylvia Stockler[b], Hilary Vallance[a].
[a]Department of Pathology and Laboratory Medicine, BC Children's Hospital, Vancouver, BC, Canada. [b]Dept of Pediatrics, BC Children's Hospital, Vancouver, BC, Canada.
Case report: A 5 year old boy with normal intelligence presented with headache and lower back pain during an acute viral illness. Physical exam was unremarkable. Investigation revealed mild but persistent hypertransaminasemia: ALT 56, 78 (10 – 25 U/L) and AST 74, 89 (15- 50) with mild hyperferritinemia 45 (9 – 30 ug/L) prompting further metabolic investigation.
Methods: Plasma amino acids were measured by UPLC-MS/MS. Plasma S-Adenosylmethionine (SAM) and S-Adenosylhomocysteine (SAH) were measured at the Baylor Institute of Metabolic Diseases, Dallas,TX. GNMT gene sequencing was performed at Baylor College of Medicine, Houston,TX.
Results: Plasma methionine was markedly elevated on three occasions ranging from 450-650 umol/L (ref range 5-40 umol/L). Total homocysteine was normal excluding cystathionine b-synthase deficiency. Plasma SAM was markedly elevated 2840 nmol/L (ref range 33-95) and SAH was slightly increased 46 nmol/L (13-28 nmol/L). GNMT gene sequencing revealed compound heterozygosity for a known pathogenic mutation, c.529C>A, and a novel mutation, c.431C>T, predicted to be pathogenic by Polyphen2 and SIFT.
Conclusion: We report a new case of GNMT deficiency in a patient with mildly elevated liver transaminases. To date there have been only 3 GNMT deficiency cases reported in the literature. All presented with mildly elevated liver transaminases in childhood. This diagnosis raises several questions: Is GNMT deficiency underdiagnosed? Should plasma amino acids tests be ordered in the context of unexplained and persistently elevated liver transaminases? What is the long term prognosis of patients with GNMT deficiency? Current clinical status of the three previously reported GNMT patients will be presented.
Keywords: methyl transferases, Inborn Errors of Metabolism (IEM), liver, prognosis

P115 The N-acetylneuraminate pyruvate lyase (NPL) gene: a novel cause of free sialic aciduria but is there a clinical phenotype?
Bojana Rakić[a], Dorrit Hansen[a], Graham Sinclair[a], Anna Lehman[c], Hilary Vallance[a], Clara D. van Karnebeek[b,d,e].
[a]Department of Pathology and Laboratory Medicine, BC Children's Hospital. [b]Dept of Pediatrics, BC Children's Hospital. [c]Department of Medical Genetics, University of British Columbia. [d]Treatable Intellectual Disability Endeavour In B.C. (TIDE BC). [e]University of British Columbia.
Introduction: Our Omics2TreatID study aims to identify novel inborn errors of metabolism (IEMs) via a combined genomics and metabolomics approach. We studied a 19 year old, cognitive normal male born to non-consanguineous Filipino parents with progressive dilated cardiomyopathy, mild skeletal myopathy and sensorineural hearing loss; extensive metabolic investigations revealed marked free sialic aciduria, confirmed by 2 independent reference laboratories. Known genetic causes of free sialic aciduria as well as cardiomyopathy were ruled out by molecular analysis.
Method and Results: Whole exome sequencing revealed compound heterozygous rare, damaging mutations in *NPL* encoding N-acetylneuraminate pyruvate lyase (NPL) which controls the final step of sialic acid metabolism by catalyzing the conversion of sialic acid into N-Acetylmannosamine and pyruvate. Sanger sequencing confirmed carrier status in parents and the same *NPL* mutations in his unaffected older sibling, who also was found to have marked free sialic aciduria. In the index case, no pathogenic variants were found in the known cardiomyopathy genes, but did identify *GJB2* (connexin 26) compound heterozygous mutations previously reported to cause sensorineural deafness.
Conclusion: To date, two known IEMs associated with free sialic aciduria have been reported; lysosomal *SLC17A5* which causes Salla and ISSD disease and *GNE* which causes cytosolic free sialic acid accumulation and a milder clinical phenotype. Our report of recessive *NPL* mutations adds a third genetic condition to the differential diagnosis of free sialic aciduria. Functional validation is ongoing. Identification of additional cases will be needed to confirm causality and understand the clinical phenotype of NPL deficiency.
Keywords: Inborn Errors of Metabolism (IEM), genomics, Whole Exome Sequencing (WES), discovery
Funding: This work was supported by funding from the B.C. Children's Hospital Foundation as "1st Collaborative Area of Innovation" (www.tidebc.org); Genome BC (SOF-195 grant); Genome BC and Genome Canada grants 174CDE (ABC4DE Project); and the Canadian Institutes of Health Research #301221 grant.

P116 Cross Canada approaches to the common Arctic variant (P479L) in CPT1A deficiency- how can we achieve consensus?
Cheryl Rockman-Greenberg[a], Jessica Hartley[a], Graham Sinclair[b], Pranesh Chakraborty[c], Bob Thompson[d], Hilary Vallance[b], Laura Arbour[e], Sorcha Collins[b], Dennis Bulman[c].
[a]University Of Manitoba. [b]University of British Columbia. [c]Children's Hospital of Eastern Ontario, University of Ottawa. [d]Cadham Provincial Laboratory. [e]University of Victoria.
Untreated classic CPT1A deficiency leads to hypoglycemia, seizures, and early death. In contrast, the CPT1A P479L variant has only reduced activity, but may still be associated with hypoglycemia. P479L is seen only in Inuit, Inuvialuit, Alaska Native and Vancouver Island First Nations (FN) populations. Significant association of the P479L allele and infant mortality (IM) has been established, but not causation. There is substantial controversy if there is a role for newborn screening. We present different approaches in the respective aboriginal populations in BC, Manitoba and Ontario. Given the high prevalence of P479L in FN of Vancouver Island, BC (>20% homozygosity), Medical Guidelines to Prevent Hypoglycemia have been developed. Similarly, Manitoba

specialists covering Kivalliq, Nunavut (>70% homozygosity) have focused on increasing awareness locally, Kivalliq newborns born in Winnipeg are screened for hypoglycemia at 1 hour and P479L genotyping is performed on all Inuit newborn screens with abnormal acylcarnitine profiles or symptomatic hypoglycemia. Newborn screens on Inuit babies from the Baffin region born in Ottawa or in the Baffin region are performed by Newborn Screening Ontario (NSO); babies whose second tier genotyping confirms P479L homozygosity are considered "screen negative" as clinical significance and intervention are still felt to be unproven. These different approaches demonstrate the need for more research to address if P479L has a negative impact on IM. In the meantime the different approaches in BC and Manitoba where all infants are considered "as if they are homozygous for P479L and potentially at risk for hypoglycemia" serve to inform and aim to mitigate potential risk. These approaches could serve as interim models for other Arctic populations awaiting further evidence to direct next steps in newborn screening.

P117 Retrospective analysis supports algorithm as efficient diagnostic approach to treatable intellectual developmental disabilities

Bryan Sayson BA[a,b,c,f], Marioara A. Moisa Popurs MD[b,c,d], Mirafe Lafek MD[b,c,d], Ruth Berkow BSc MD[c], Sylvia Stockler-Ipsiroglu MD PhD[b,c,d,e,f], Clara D.M. van Karnebeek MD PhD FRCCMG[b,c,d,e,f,g,h].
[a]Division of Pediatric Neurology, BC Children's Hospital. [b]Department of Pediatrics, BC Children's Hospital. [c]Treatable Intellectual Disability Endeavour in British Columbia. [d]Division of Biochemical Diseases, BC Children's Hospital. [e]Child and Family Research Institute. [f]University of British Columbia. [g]Centre for Molecular Medicine and Therapeutics Vancouver, Canada. [h]Michael Smith Foundation for Health Research Scholar.

Background: Intellectual developmental disorders (IDD) affect 2.5% of the population and are associated with considerable morbidity and healthcare costs. Inborn errors of metabolism (IEM) currently constitute the largest group of genetic defects amenable to causal therapy. The evidenced-based TIDE protocol comprises a first-tier 'screening step' of routine metabolic tests applied in all unexplained IDD patients. The second-tier comprises specific tests indicated by clinical phenotype, and is supported by an App (www.treatable-ID.org).
Objective: To ascertain the cost- and time-effectiveness of the TIDE protocol in patients identified with a treatable IEM at British Columbia Children's Hospital (BCCH).
Methods: Retrospective review of all IDD patients diagnosed with a treatable IEM (2000-2009) at BCCH. Data on IEM type, clinical phenotype, diagnostic trajectory were collected. Total diagnostic costs and time-intervals between initial presentation and IEM identification were compared to the TIDE protocol model.
Results: 31 patients (16 male) were diagnosed with treatable IDD from 2000-2009. For those identifiable via the 1st tier (n=20), the average cost-savings would have been $311.17 CAD, and via a second-tier test (n=11) $340.14 CAD. A mean diagnostic delay of 9 months (range 1-29 months) could have been avoided in 9 patients with first-tier diagnoses. For those with second-tier treatable IDD, the Treatable IDD App may have yielded diagnoses more rapidly.
Conclusion: The TIDE protocol for treatable IDD appears to reduce diagnostic delay and costs. Early diagnosis is essential to initiate treatment and avoid brain damage. Larger prospective studies are underway to generate more evidence in support of this novel approach.
Funding: This work was supported by funding from the BC Children"s Hospital Foundation as "1st Collaborative Area of Innovation" (www.tidebc.org). CvK is the supported as Scholar by the Michael Smith Foundation for Health Research.

P118 Defects in fatty acid amide hydrolase 2 in a male with neurologic and psychiatric symptoms and vertical gaze palsy

Sandra Sirrs[a], Clara van Karnebeek[b,c,d], Xiaoxue Peng[e], Casper Shyr[c], Maja Tarailo-Graovacc[d,j], Rupasri Mandal[f], Daniel Testa[g], Devin Dubin[g], Gregory Carbonetti[h], Steven E. Glynn[e], Wendy P. Robinson[j], Beomsoo Han[f], David Wishart[f], Colin J. Ross[j], Wyeth W. Wasserman[j], Trevor A. Hurwitz[k], Graham Sinclair[l], Martin Kaczochae[i].
[a]Department of Medicine, University of British Columbia, Vancouver, Canada. [b]Department of Pediatrics, University of British Columbia, Vancouver, Canada. [c]Centre for Molecular Medicine and Therapeutics, Vancouver, BC. [d]Treatable Intellectual Disability Endeavour in British Columbia (TIDE-BC). [e]Department of Anesthesiology, Stony Brook University, Stony Brook, NY. [f]Departments of Biological and Computing Sciences, University of Alberta, Edmonton, Canada. [g]Half Hollow Hills High School, Dix Hills, NY. [h]Graduate Program in Molecular and Cellular Biology, Stony Brook University, Stony Brook, NY. [i]Department of Biochemistry and Cell Biology, Stony Brook University, Stony Brook, NY. [j]Department of Medical Genetics, University of British Columbia, Vancouver, Canada. [k]Department of Psychiatry, University of British Columbia, Vancouver, Canada. [l]Department of Pathology and Lab Medicine, University of British Columbia, Vancouver, Canada.
Objectives: Fatty acid amide hydrolase 2 (FAAH2) is a hydrolase that mediates the degradation of endocannabinoids in man. Alterations in the endocannabinoid system are associated with a wide variety of neurologic and psychiatric conditions but the phenotype and biochemical characterization of patients with genetic defects of FAAH2 activity have not previously been described. We sought to define the clinical phenotype of a patient with a functional defect in FAAH2.
Design and Methods: We used whole exome sequencing to identify the mutation in FAAH2 and a variety of proteomic, biochemical and lipidomic techniques were used to define the effects of the mutation on the biochemistry of the patient and the impact of the mutation on protein function.
Results: We describe a male with autistic features which onset before the age of 2 years who subsequently developed additional features including anxiety, pseudoseizures, ataxia, supranuclear gaze palsy, and isolated learning disabilities but was otherwise cognitively intact as an adult. Alterations in lipid metabolism with abnormalities of the whole blood acyl carnitine profile were found. Whole exome sequencing identified a rare missense mutation in FAAH2, which was confirmed by Sanger sequencing. We demonstrate that this mutation results in partial inactivation of the FAAH2 protein and altered levels of endocannabinoid metabolites.
Conclusions: We propose that genetic alterations in FAAH2 activity contribute to neurologic and psychiatric disorders in humans.

P119 Lag time to benefit for adult Fabry disease patients on agalsidase beta enrolled in the Fabry Registry

David Warnock[a] , Daniel G Bichet[b] , Ademola Abiose[c], Gustavo Cabrera[d], Joel Charrow[e], Dominique P. Germain[f], Robert J. Hopkin[g], Ana Jovanovic[h], Aleš Linhart[i], Sonia S. Maruti[j], Michael Mauer[k], Manesh R. Patel[l], Juan Polite[m], Stephen Waldek[n], Christoph Wanner[o], Han-Wook Yoo[p], Alberto Ortiz[q].
[a]Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL, USA. [b]Department of Medicine, Hôpital du Sacré-Coeur de Montréal and University of Montreal, Montreal, QC, Canada. [c]North Ohio Heart Center, Westlake, Ohio, USA. [d]Departamento de Ecocardiografía, Grupo Medico Del Viso, Buenos Aires, Argentina. [e]Division of Genetics, Birth Defects and Metabolism, Ann and Robert H. Lurie Children's Hospital of Chicago, IL, USA. [f]Division of Medical Genetics, University of Versailles – St Quentin en Yvelines, Versailles, France; Assistance Publique – Hôpitaux de Paris, Garches, France. [g]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. [h]Department of Endocrinology and Metabolic Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom. [i]Department of Internal Medicine, School of Medicine, Charles University, Prague, Czech Republic. [j]Genzyme, a Sanofi Company, Cambridge, MA, USA. [k]Departments of Pediatrics and Medicine, University of Minnesota, Minneapolis, MN, USA. [l]Division of Cardiovascular Medicine, Duke University School of Medicine, Durham, North Carolina, USA. [m]Department of Neurology, Fundacion Para el Estudio de Enfermedades Neurometabolicas (FESEN), Buenos Aires, Argentina. [n]Independent Medical Consultant (retired from Salford Royal

NHS Trust 2011). [o]Division of Nephrology, University Clinic, University of Würzburg, Würzburg, Germany. [p]Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea. [q]Unidad de Dialisis, IIS-Fundacion Jimenez Diaz/UAM, IRSIN, Madrid, Spain.

Objectives:Agalsidase beta is an enzyme replacement therapy for Fabry disease, a genetic disorder characterized by low α-galactosidase A activity, accumulation of glycosphingolipids, and life-threatening cardiovascular, renal and cerebrovascular events. In clinical trials agalsidase beta cleared endothelial glycolipid deposits within 6 months. We hypothesized that agalsidase beta takes time to benefit patients (i.e., "lag time to benefit") and analyzed severe clinical events as our endpoint.

Design and Methods: The incidence rate of severe clinical events (renal failure, cardiac events, stroke and death) was studied in 1,133 Fabry adults (706 males, 427 females) enrolled in the Fabry Registry (NCT00196742; supported by Genzyme, a Sanofi company) who received agalsidase beta (average dose 1 mg/kg/2 weeks) for up to 5 years. Patients with known late-onset genetic variants or polymorphisms were excluded.

Results: The incidence rate for all events was 110 per 1000 person-years (95% CI: 84-143) in the first 6 months, was halved thereafter to 44 to 56 events per 1000 person-years over subsequent intervals up to 5 years. The greatest incidence rate decline was among males and patients ages ≥40 years.

Conclusions: Contrary to the expected natural history increasing rates of severe clinical events over time, adult patients with Fabry disease experience a decrease in severe clinical events after 6 months of agalsidase beta treatment. This 6-month time lag to benefit is consistent with time to clearance of glycolipid deposits as observed in clinical trials. Follow-up beyond 5 years is needed

Keywords: Fabry disease, agalsidase beta, clinical events, time lag

Funding: This research was funded by Genzyme, a Sanofi company.

P120 Uncovering novel genetic variants in a consanguineous family with pyridoxine-dependent epilepsy

H. Al Shekaili[a], C. van Karnebeek[a], K. Al Thihli[b], C. Ross[a], M. Tarailo-Graovac[a], M. Coulter-Makie[a], X. Han[a], M. Higginson[a], L. Zhang[a], J. M. Friedman[a].

[a]Child & Family Research Institute, University of British Columbia, Vancouver BC, Canada. [b]Genetic and Developmental Medicine Clinic, Sultan Qaboos University Hospital, Muscat, Oman.

Background: Pyridoxine-responsive epileptic encephalopathies (PREE) represent a clinically and genetically heterogeneous group of rare, autosomal recessive disorders[1,2]. They are characterized by recurrent seizures in the prenatal, neonatal, or postnatal period, which are typically resistant to conventional anticonvulsant treatment but show remarkable response to the administration of pyridoxine (vitamin B6) [1,3,4,5]. The prototypical example of these inborn errors of metabolism is pyridoxine-dependent epilepsy (PDE), a neonatal seizure disorder with an estimated incidence of 1:100,000 to 1:750,000[6]. In most affected infants, PDE is caused by mutations in the antiquitin gene *(ALDH7A1)*[7] and subsequent inactivation of α-aminoadipic semialdehyde dehydrogenase (antiquitin, ATQ), an enzyme that functions within the cerebral lysine catabolism pathway, leading to accumulation of α-aminoadipic semialdehyde (α-AASA)[6]. α-AASA is in spontaneous equilibrium with Δ1-piperideine-6-carboxylic acid (P6C) and is oxidized by ATQ to α-aminoadipic acid, which is eventually oxidized to produce acetyl CoA. Deficiency of ATQ causes seizures because accumulating P6C condenses with pyridoxal 5'-phosphate (PLP) and inactivates this enzyme cofactor, which is essential for normal metabolism of neurotransmitters[7]. Although *ALDH7A1* is the only gene for which mutations are known to cause PDE, locus heterogeneity has been demonstrated, other genes appear to be responsible in some families[8]. About 5% of infants with clinically typical PDE have no detectable mutation of *ALDH7A1*[9].

Objectives: This study was carried out to characterize the genetic defect underlying PREE in three consanguineous Omani Arab families with total of four affected children who have a PDE-like clinical picture but negative ATQ biomarkers.

Materials and Methods: In the first family, whole-genome SNP genotyping was performed on the father and the two affected children using Illumina HumanOmni5-Quad array chip. Based on the obtained high density SNP dataset, genome-wide runs of homozygosity (RoH) mapping was carried out using SNP & Variation Suite (SVS) software version 8.1.0 (Golden Helix). Whole-exome sequencing (WES) was carried out on the mother and affected sib by Perkin-Elmer (Waltham, Massachusetts).

Results: After analysis of WES results, 38 homozygous recessive (HR), 11 compound heterozygous, and 342 homozygous de novo variants have passed the multiple filtering steps of the implemented pipeline. Eleven of the 38 HR candidate genes had genomic coordinates that overlapped or fell in close proximity with the previously mapped RoH in this family (Fig. 4). Of these 11, 2 genes were prioritized as top candidates based on their functional relevance. The first gene belongs to the solute carrier (SLC) family of genes. Three members of the SLC super family have been already described as vitamin transporters. To date, no transporter for vitamin B6 has been identified in humans despite multiple experimental evidence indicating the existence of an efficient and specific carrier-mediated mechanism of vitamin B6 uptake by human cells[10,11,12]. The second candidate gene encodes a peptidase enzyme which was described to cleave a neuropeptide that is expressed both in the central nervous system and in the periphery and is thought to function as a neurotransmitter.

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P121 Suspected beta-ureidopropionase deficiency in two siblings with typical clinical and biochemical features: demonstrating the effectiveness of the TIDE-BC protocol

Katherine A. Blood[a], Hilary Vallance[b], Ramona Salvarinova[c], Clara D. van Karnebeek[c], Margaret L. McKinnon[a].

[a]Department of Medical Genetics, University of British Columbia, Vancouver, BC. [b]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC. [c]Division of Biochemical Diseases, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, BC.

Background: Beta-ureidopropionase deficiency is a rare disorder of pyrimidine degradation characterized by N- carbamyl-beta-alanine and N-carbamyl-beta-aminoisobutyric aciduria. There are fewer than 30 genetically confirmed patients reported with this autosomal recessive condition caused by mutations in the *UPB1* gene. The presentation is highly variable, from asymptomatic individuals to patients with severe neurological involvement. Common findings include MRI abnormalities, microcephaly, seizures and intellectual disability. Currently there is no proven treatment.

Case report: We present two siblings with typical clinical and biochemical features of beta-ureidopropionase deficiency. The proband, last seen at 3.5 years, has been followed since birth for microcephaly, growth retardation, global developmental delay and mild dysmorphisms. MRI at 2 years showed dilated ventricles, prominent cortical sulci and incomplete myelination. Biochemical and genetic investigations were inconclusive, until enrolled in the TIDE-BC protocol which is a 2-tiered diagnostic algorithm to enhance early diagnosis of inborn errors of metabolism in patients with intellectual disability. Routine 1st tier screening with urine purine and pyrimidine analysis revealed significantly elevated N-carbamyl-beta-alanine: 280 (repeat 212) micromol/mmol creatinine (reference range 2-60) suggestive of beta-ureidopropionase deficiency. The proband's younger sibling, with a similar clinical phenotype, also had elevated N-carbamyl-beta-alanine: 323 micromol/mmol creatinine. However, sequencing of *UPB1* did not identify pathogenic mutations in the coding region or intron/exon boundaries; further molecular and biochemical studies are underway.

Conclusions: We present siblings with biochemical findings and a clinical phenotype consistent with beta-ureidopropionase deficiency

but with absent *UPB1* mutations. The absence of detectable *UPB1* mutations may indicate a novel genetic mechanism for N-carbamyl-beta-amino aciduria.
Keywords: pyrimidines, beta-ureidopropionase, *UPB1*, diagnosis, discovery

P122 Phosphorus Magnetic Resonance Spectroscopy in Evaluation of Heteroplasmy and Response to Exercise in a Family with MELAS
Csilla Egri[a], Alex McKay[b], Trudy Harris[b], Sandra Sirrs[c], Gabriella Horvath[c].
[a]MD Undergraduate Program, Faculty of Medicine, University of British Columbia. [b]MRI Research Center, Faculty of Medicine, University of British Columbia. [c]Adult Metabolic Clinic, Vancouver General Hospital.
Objectives: This study evaluates the utility of 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS) in inferring mitochondrial heteroplasmy amongst family members with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), as well as changes to muscle bioenergetics in response to an exercise program.
Methods: Participants included two controls and three family members aged 20, 23, and 50 with mitochondrial A3243G mutation. Genetic testing revealed 90, 45, and 30% heteroplasmy respectively. The 23 year old was clinically unaffected. MR spectra was obtained from the calf muscles at rest, during a foot petal exercise and exercise under ischemic conditions. Phosphocreatine (PCr), inorganic phosphate (Pi), and adenosine diphosphate (ADP) peaks were used to calculate respective concentrations, pH and mitochondrial ATP synthesis rate (Q/Q_{max}). Muscle MRS was repeated after completing a one-month exercise program.
Results: The patient with 45% heteroplasmy had similar results on MR spectra to control. The patient with 90% heteroplasmy had proportionally reduced PCr, especially in the exercising muscle. Overall Pi and ADP were highest in those clinically affected. The low PP in patients also indicates low energy reserve at rest, and the increased Q/Q_{max} measures increased mitochondrial capacity and accelerated ATP production. The exercise program improved PCr in the 50 year old (30%) although it did not improve the ADP and Pi levels.
Conclusion: Muscle MRS can assess severity of muscle disease in MELAS, and shows that heteroplasmy relates to MR spectra in an age-dependent manner. The intensity of the exercise program in this study was likely not high enough to produce significant improvements.
Keywords: muscle magnetic resonance spectroscopy, MELAS, heteroplasmy
Funding: Rare Disease Foundation grant number F12-02634

P123 Long Term Dietary and Laboratory Monitoring of Four Patients with Propionic Acidemia
Csilla Egri[a], Carol Hartnett[b], Keiko Ueda[b], Sylvia Stockler[b], Gabriela Horvath[b].
[a]MD Undergraduate Program, Faculty of Medicine, University of British Columbia, Vancouver, BC. [b]Department of Biochemical Diseases, BC Children's Hospital, Vancouver, BC.
Objectives: Differing opinions exist on the appropriate dietary management of Propionic Acidemia (PA). We evaluated the effect of dietary management strategies on clinical and laboratory outcomes of four pediatric PA patients.
Methods: Retrospective chart review inclusive of 1999-2007 of four PA patients ages 0-8 years. Dietary data included natural protein/kg/day, amino acid (AA) mixture/kg/day and total protein/kg/day. Dietary recommendations were compared with Ross (Nutr Supp Prot 2001;4:230-261) and Sass (Clin Ped 43;9:837-843). Laboratory results included ammonia and plasma amino acids, recorded as within or outside age appropriate reference ranges. Sick days, defined as ammonia >60 micromol/L, were excluded from analysis.
Results: Branched chain amino acids (especially valine) were found to be consistently low despite extra supplementation. AA mixture intake was above literature recommendations. The median (g/kg) dietary protein and natural protein/AA mixture did not meet minimum recommendations for natural protein intake in all age groups except <12 months old. Maintaining a diet within recommendations for AA mixture and total protein appeared to increase the percentage of times valine and leucine fell within reference ranges, with little effect for natural protein alone.
Conclusion: Natural protein intake was over restricted compared to literature recommendations. We conclude that dietary treatment in PA should contain a balanced ratio of natural protein and AA mixture. Natural protein should meet the lower limit of the recommended values in all age groups, with addition of AA mixture to achieve adequate growth and normal laboratory values, with careful monitoring of laboratory parameters suggestive of metabolic decompensation.
Keywords: propionic acidemia, dietary management, branched chain amino acids

P124 Mania following acute decompensation in ornithine transcarbamylase deficiency
Adeline Jacquinet[a,b], Sandra Sirrs[c], Andre Mattman[c], Anna Lehman[a,c].
[a]Department of Medical Genetics and Child and Family Research Institute, University of British Columbia, Vancouver, BC V6H 3N1, Canada. [b]Department of Genetics, University of Liège, Liège, Belgium. [c]Adult Metabolic Diseases Clinic, Vancouver, Canada.
Background: Ornithine transcarbamylase deficiency is the most common urea cycle disorder and presents an X-linked pattern of inheritance. Both males and females may be affected with variation in severity and age of onset. Psychiatric symptoms, including episodic psychosis, atypical depression, confusion, erratic behavior or delirium, are possible presentations of late-onset disease. Manic behaviors have previously been reported with hyperammonemia induced by valproic acid. Usually, psychiatric behaviors cease with normalization of ammonia levels.
Case Report: We report a family with two males with confirmed late-onset OTC deficiency (and other adult males with unexplained lethal encephalopathy) due to a missense mutation in OTC (c.119G>A; p.R40H). One 29-year-old male individual, with no psychiatric history, presented hypomanic symptoms with a significant shift from his personality in the days following his first major episode of acute decompensation. Ammonia levels were measured as 245, 30, 11, 106, 20, 38 and 17 micromol/L on days 2, 5, 8, 9, 9, 9, and 10, respectively, following the acute crisis onset. Symptoms of vomiting, confusion, tremors and loss of consciousness stopped at day 5.
Hypomanic symptoms were noted from day 5 and were finally controlled with long-acting quetiapine ten days after normalization of serum ammonia levels (daily levels were normal from day 10 to day 21). CT scan of the brain was normal.
Conclusion: Illustrated by this case report, occurrence of mania secondary to a hyperammonemic crisis may be the consequence of dysregulated neurotransmission balance in brain, which can persist after normalization of serum ammonia levels.
Keywords: ornithine transcarbamylase deficiency, mania, psychiatric disorder
Funding: AJ is supported by grants from Wallonia Brussels International and from the Léon Fredericq Fund

P125 IEMBASE, knowledgebase and online mini-expert system for Inborn Errors of Metabolism
Jessica Lee[a,b,e], Clara D. van Karnebeek[a,c], Wyeth W. Wasserman[a,d], Nenad Blau[e].
[a]Centre for Molecular Medicine and Therapeutics; Child and Family Research Institute, Vancouver, BC, Canada. [b]Genome Science and Technology Graduate Program, University of British Columbia, Vancouver, BC, Canada. [c]Division of Biochemical Diseases, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, BC, Canada. [d]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada. [e]Division of Metabolism, University Children's Hospitals, Heidelberg, Germany and Zürich, Switzerland.
Objectives: Early and accurate diagnosis is essential in cases of inborn errors of metabolism (IEMs). It allows for a timely initiation of therapies, which can significantly improve patient outcomes. The accuracy and timeliness of IEM diagnoses, however, are often hampered by the heterogeneity of symptoms, as well as extensive skills and required knowledge on 500+ IEMs in order to properly interpret patient profiles in the context of their phenotypes. To address this problem, we have developed an online system which combines an expert knowledgebase and a smart system to support efficient diagnosis and management for clinicians.
Design and Methods: We extracted disease-characterizing profiles of clinical symptoms and biochemical markers from an expert-generated database of 500+ IEMs. These profiles were then mapped to the Human Phenotype Ontology and Logical Observation Identifiers Names and

Codes in order to exploit the semantic relationships of symptoms from the profiles. This, in turn, allows the smart system to algorithmically determine a tiered list of possible IEMs which match the user-provided symptoms.
Results: The IEMBASE accepts an array of biochemical markers and clinical symptoms from a user and returns a ranked list of possible IEMs that match the input profile. In addition, the system can explain the rationale of its results, suggest possible tests, list possible treatment options, and provide access to its database of biochemical, molecular, and clinical information.
Conclusions: We expect that this unique system dedicated to IEMs will significantly improve clinical practice to benefit outcomes of patients and families suffering these rare diseases.
Keywords: Diagnosis-support System, Expert Knowledgebase, Inborn Errors of Metabolism
Funding: RD-CONNECT and TIDE-BC (1st Collaborative Area of Innovation, BC Children's Hospital Foundation 2011-16)

P126 A retrospective review of hematologic factors influenced by the ketogenic diet; investigating potential macrocytic anemia and neutropenia

Bryan Sayson[a], Clara van Karnebeek[a], James Lee[a].
[a]University of British Columbia.

Background: The ketogenic diet is high-fat, low-carbohydrate and low-protein diet and is an effective non-pharmaceutical based treatment for epilepsy. While the mechanism for it's efficacy is still not well understood, the effects of this diet have been evaluated by many other studies. However, the effect on hematologic indices is yet to be fully elucidated. Macrocytosis, or a Mean Corpuscular Volume (MCV) >100 fL, has been observed in clinical cases when ketogenic diet is administered. Furthermore, a case of fatal decline in neutrophil level had been observed at this facility in recent years.
Methods: This study retrospectively reviewed patients on the Ketogenic Diet from 2007-2014 for hematologic variations, specifically macrocytosis, leukocyte, particularly neutrophil, reduction and triglyceride levels. Comparison was made at intervals of 3, 6, 12 and 18 months.
Results: In our cohort of 88 patients (46 female), mean Neutrophil levels were 3.32, at baseline and decreased by 0.76, 0.52, 0.48 and increased by 0.38 from baseline at 3, 6, 12, and 18 months, respectively. Mean MCV increased by 2.22, 4.93, 4.82, and 5.70 from baseline at corresponding intervals. Mean MCV, overall, did not increase above 100 fL.
Conclusion: While the mean increase in MCV did not exceed 100 fL, several patients displayed macrocytic levels. Neutrophil count declined at 3, 6, and 12 but recovered at 18 months. The initial findings of this study suggest that further prospective studies should be conducted to elucidate any true effects on hematologic indices caused by the ketogenic diet.

P127 Targeted batch analysis for urine organic acidopathies

Lorne E Seargeant PhD FCACB[a,b], Catherine Mallory BSc MLT[b].
[a]Pediatrics & Child Health, University of Manitoba, Winnipeg, MB.
[b]Diagnostic Services of Manitoba, Winnipeg, MB (DSM).

Objectives: To evaluate the suitability of GC-APCI-TOF-MS (Gas Chromatography, Atmospheric Pressure Chemical Ionization, Time-of-Flight, Mass Spectrometry) for detection of urine organic acidopathies.
Background: Urine organic acid analyses for the detection of inborn errors of metabolism have traditionally been performed by extraction, TMS (TriMethylSilyl) derivatization, and analysis on a quadrupole mass spectrometer equipped with an electron impact source. The fragmentation patterns require a lot of time for analysis, and a high level of technical expertise for interpretation.
Design and Methods: Urine samples were prepared, as usual, for analysis on a Bruker Daltonics GC-APCI-TOF-MS instrument. The organic acid target compound list included the organic acid name, molecular formula, and retention time for 92 selected organic acids. Target and quantitative analysis was performed using Bruker TASQ software. Quality of organic acid identification was scored by the software, for all samples, by the differences in measured versus calculated monoisotopic mass/charge ratio), mass isotopic ratio, and retention time.
Results: Testing by GC-APCI-TOF-MS was performed in 2 laboratories (Bruker, DSM) on 3 mixtures of CAP proficiency-testing organic acid samples. All organic acid disorders were identified in both laboratories. In-house testing on patient samples were also concordant with analyses performed at Mayo Medical Laboratories. Automated batch processing using TASQ and Access/VBA provided for a greatly decreased time for data analysis.
Conclusions: The quality of urine organic acid analysis for disorders of organic acid metabolism by GC-APCI-TOF-MS appears to be as good as or better than traditional analysis, and provides for significantly improved interpretation time.

P128 The little things that matter: A qualitative study of the disease management experiences of caregivers of children with inherited metabolic diseases

Shabnaz Siddiq[a], Brenda J. Wilson[a], Ian D. Graham[a], Monica Lamoureux[b], Sara D. Khangura[a], Kylie Tingley[a], Laure Tessier[a], Sarah Wafa[c], NataliyaYuskiv[d], Pranesh Chakrabortyx[b], Anne-Marie Laberge[e], Chitra Prasad[f], Fiona A. Miller[g], John J. Mitchell[c], Kathy N. Speechley[j], Komudi Siriwardena[g], Yannis Trakadis[c], Rebecca Sparkes[j], Alette Giezen[d], Jagdeep Walia[k], Robin Hayeems[g,h], Shailly Jain[l], Cheryl Greenberg[m], Beth K. Potter[a].
[a]School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, ON. [b]Newborn Screening Ontario, Children's Hospital of Eastern Ontario (CHEO), Ottawa, ON. [c]McGill University Health Centre, The Montreal Children's Hospital, Montréal, QC. [d]BC Children's Hospital, University of British Columbia, Vancouver, BC. [e]CHU, Hôpital Sainte-Justine, Montréal, QC. [f]London Health Sciences Centre, London, ON. [g]Hospital for Sick Children, University of Toronto, Toronto, ON. [h]Program in Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON. [i]LHSC London, Western University, London, ON. [j]Alberta Children's Hospital, University of Calgary, Calgary, AB. [k]Kingston General Hospital, Queen's University, Kingston, ON. [l]Stollery Children's Hospital, University of Alberta, Edmonton, AB. [m]Department of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, MB.

Objectives: We sought to understand the experiences of caregivers of children with inherited metabolic diseases (IMD), regarding the management of disease, its impact on child and family life, and interactions with the health care system.
Design and Methods: At three participating centres, we are inviting caregivers of children with an IMD who are enrolled in the Canadian Inherited Metabolic Diseases Research Network to participate in a semi-structured telephone interview. Participants are selected with the aim of achieving a diverse sample with respect to treatment centre, IMD, and age. Interviews explore participants' experiences, emphasizing impacts of the disease and its treatment on the child and family, and explicitly querying perceptions of interactions with the health care system. Data are being analyzed using qualitative description to identify emerging themes.
Results: Recruitment is ongoing. Fourteen participants have been interviewed, with nine of these interviews incorporated into our analysis to date. Preliminary findings suggest that families adapt; daily disease management protocols that are often complex become routine. As well, interactions with their most involved health care providers are typically described as positive. However, caregivers are often concerned about social challenges faced by their children, particularly for those where dietary restrictions are part of treatment. They also report stress resulting from certain interactions with the health care system; these are not specific to IMDs and include emergency department and laboratory service encounters.
Conclusions: As described by one participant, *"it's very, very small things that make a massive difference in overall patient care".*
Keywords: inherited metabolic diseases (IMD), qualitative study, family impact, quality of life
Funding: Canadian Institutes of Health Research (CIHR) Emerging Team Grant, 2012-2017 (B Potter, P Chakraborty et al).

P129 Expanding the Clinical Spectrum of Myopathy, Lactic Acidosis and Sideroblastic Anemia-type 2 (MLASA2)

Kyra E. Stuurman MD[a,b], Kathryn Selby MD[c], Florin Sasarman PhD[d], Lorne Clarke MD[a], Andre Mattman MD[e], Margaret L. McKinnon MD[a].
[a]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada. [b]Department of Clinical Genetics, VU University Medical Center, Amsterdam, The Netherlands. [c]Division of Neurology, Department of Pediatrics, BC Children's Hospital, Vancouver, BC, Canada. [d]Montreal Neurological Institute and Department of Human Genetics, McGill University, Montreal, QC, Canada. [e]Department of Pathology, Vancouver General Hospital and St Paul's Hospital, Vancouver, BC, Canada.

Background: MLASA is a rare autosomal recessive mitochondrial disorder characterized by myopathy, lactic acidosis and sideroblastic anemia with variable severity. Mutations have been described in *PUS1* (type 1) and *YARS2* (type 2) genes. Although progressive dysphagia is common, severe gastrointestinal issues have only been reported in one patient with a confirmed *YARS2*-mutation.

Case: We describe a patient with MLASA-type 2 with severe early gastrointestinal concerns. At age seven, this healthy developmentally-normal girl, of non-consanguineous parents, presented with daily abdominal pain, loose stools and low hemoglobin. Extensive gastrointestinal work-up did not identify a cause for her symptoms. Transfusion dependent anemia (45 g/l) and unexplained abdominal pain persisted. She developed increasing exercise intolerance and assessment at age 12 revealed thin musculature, marked fatigability and extremely high lactate levels. By age 14, she was mainly non-ambulatory. She was diagnosed with mitochondrial myopathy, persistently high lactate levels (12-15 mmol/l), and muscle biopsy showing ragged red fibers and profound complex IV deficiency (144 nmol/min/mg). She exhibited increasing respiratory compromise, became ventilator-dependent and died at age 15. Bone marrow biopsy confirmed sideroblastic anemia, and clinical diagnosis of MLASA. *PUS1*-gene sequencing was normal. Recent post-mortem molecular testing revealed a novel *YARS2*-mutation, c.98C>A, p.Ser32X, predicted to be protein-truncating and damaging. Extended analysis is underway for the second mutation.

Conclusions: We highlight this case of MLASA-type 2 to emphasize that gastrointestinal symptoms with anemia may be an important feature of this autosomal recessive mitochondrial disorder, and add a novel truncating mutation to typically missense mutations currently described in *YARS2*.

P130 Examining the genotype-phenotype relationship for patients with very-long-chain acyl CoA dehydrogenase deficiency: A systematic review

Kylie Tingley[a], Beth K Potter[a], Michael T. Geraghty[b], Julian Little[a], Lindsey Sikora[a] in collaboration with the Canadian Inherited Metabolic Diseases Research Network (CIMDRN).
[a]University of Ottawa. [b]Children's Hospital of Eastern Ontario.

Objectives: Predicting disease severity and the risk of metabolic decompensation in very-long-chain acyl CoA dehydrogenase deficiency (VLCADD) is challenging, particularly for asymptomatic newborns diagnosed through newborn screening. An inability to predict prognosis precisely may lead to overtreatment of affected infants at lower risk of adverse outcomes. Our objective is to systematically review existing evidence characterizing the genotype-phenotype relationship in VLCADD, emphasizing diagnostic and treatment implications.

Design and Methods: A combination of MeSH headings and keywords in electronic databases (Medline, Embase, The Cochrane Library, and DARE) were searched for human studies of VLCADD containing information about each patient's genotype (i.e. mutational analysis) AND phenotype (biochemical profile, clinical presentation, and/or measure of enzymatic function). Two independent reviewers screened and abstracted potentially relevant articles using a two-stage process. Logistic regression estimated the probability of having chronic or acute VLCADD symptoms based on genotype.

Results: We identified 133 unique VLCADD patients and 141 unique genetic mutations from 40 included studies. Thirteen patients had two likely pathogenic mutations, 33 patients had one likely pathogenic mutation and one mutation of unknown pathogenicity, and 82 patients had two mutations with unknown pathogenicity. We found a stronger genotype-phenotype relationship among VLCADD patients with two likely pathogenic mutations compared to patients with other mutation types; however, substantial phenotypic heterogeneity remained among patients grouped by genetic mutation type.

Conclusion: Our results indicate that, at present, genotype information alone cannot reliably predict disease severity for many VLCADD patients. Next steps include a more comprehensive literature review regarding pathogenicity for the identified genetic mutations.

Keywords: very-long-chain acyl CoA dehydrogenase deficiency; fatty acid oxidation; genotype; phenotype; systematic review

P131 Comparing patient-reported outcomes and formal neuropsychiatric assessments in patients treated with Sapropterin, the first pharmacologic agent for PKU

Nataliya Yuskiv[a], Cynthia Davis[b], Sylvia Stockler-Ipsiroglu[a].
[a]Division of Biochemical Diseases, British Columbia Children's Hospital, University of British Columbia, Vancouver, B.C., Canada. [b]Department of Psychology, British Columbia Children's Hospital, University of British Columbia Vancouver, B.C., Canada.

Sapropterin (Kuvan®), adjuvant to the diet treatment, reduces blood phenylalanine (phe), permits relaxation of the diet, and potentially improves neuropsychiatric symptoms in individuals with phenylketonuria (PKU). We noticed that formal neuropsychiatric test results do not always match with patients' perceptions. We asked patients about perceived effects of Sapropterin in semistructured interviews and compared reports with the biomarkers (blood Phe concentration), changes in Phenylalanine tolerance, and formal neuropsychiatric test results. We investigated 14 patients (9-19 years). 7/14 showed a reduction in blood phe levels (31%-61%) and 4/7 had an increase in dietary Phe tolerance (beyond growth dependent change) in response to Sapropterin. 3/4 with mild PKU and high baseline Phe intake, did not show any further increase. Neuropsychiatric test results were available from 4 biological responders and 1 non-responder. Of the responders, 2 showed an improvement in anxiety, executive function, mood/emotional control, 2 showed no change and the non-responder showed no change. 21 interviews were done either with a parent alone or patient and parent(s). 7/14 cases reported positive changes, 5 were "uncertainly positive", and 2 reported no change. Positive changes were mostly perceived in attention and anxiety, protein consumption and quality of life. Positive changes were reported only by biological responders, non-responders belonged to the "uncertain" and "no" improvement group. There were no discrepancies between parents and patients responses. Perceived changes were in line with neuropsychiatric reports in 2 cases; in 3 cases reported outcomes and formal assessments did not match.

Keywords: PKU, Sapropterin, patient-reported outcomes
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