

## Abstracts for Presentation at the RDCRN Conference on Clinical Research for Rare Diseases

*Poster Numbers will Correlate with Abstract Number Listed Below*

1. **Evaluation of acute porphyria (AP) in patients presenting to an Emergency Department (ED) with recurrent/unexplained abdominal pain.**  
Anupam Aditi, MD, UCSF, D. Montgomery Bissell, MD, UCSF
2. **Near Patient Quantification of Ammonia in Whole Blood Samples**  
Omar B. Ayyub<sup>1</sup>, Brian T. Heligman<sup>2</sup>, Gary Cunningham<sup>1</sup>, Peter Kofinas<sup>3</sup>, and Marshall Summar<sup>1</sup>  
<sup>1</sup>Genetics and Metabolism, Children's National Medical Center, Washington, DC 20010, <sup>2</sup>Material Science and Engineering, University of Maryland, College Park, MD 20740, <sup>3</sup>Fischell Department of Bioengineering, University of Maryland, College Park, MD 20740
3. **Assessment of Treatment Response by <sup>18</sup>F-Fludeoxyglucose Positron Emission Tomography (FDG-PET) in Patients with Large Vessel Vasculitis (LVV)**  
Shubhasree Banerjee<sup>1</sup>, Sara Alehashemi<sup>1</sup>, Mark A. Ahlman<sup>2</sup>, Cahid Civelek<sup>2</sup>, Elaine Novakovich<sup>3</sup>, David A. Bluemke<sup>2</sup>, Peter C. Grayson<sup>3</sup>  
<sup>1</sup>Rheumatology Fellowship and Training Branch, NIAMS, NIH, <sup>2</sup>Radiology and Imaging Sciences, Clinical Center, NIH  
<sup>3</sup>Vasculitis Translational Research Program, NIAMS, NIH  
*\*Abstract selected for an oral presentation. There will be no poster.*
4. **Utilization of a Craniofacial Malformation Patient Cohort to Identify Novel Syndromes Leading to Targeted Therapeutics Development**  
EJ Bhoj, HH Hakonarson.  
Division of Human Genetics, Center for Applied Genomics, Children's Hospital of Philadelphia  
*\*Abstract selected for an oral presentation. There will be no poster.*
5. **Respiratory Manifestations in 38 Patients with Alström Syndrome**  
Caroline Boerwinkle<sup>1</sup>, Jan D. Marshall<sup>4,5</sup>, Joy Bryant<sup>2</sup>, William A. Gahl, MD, PhD<sup>2</sup>, Kenneth N. Olivier, MD, MPH<sup>1,3</sup> Meral Gunay-Aygun, MD<sup>2</sup>  
<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>National Human Genome Research Institute, Bethesda, MD, USA, <sup>3</sup>National Heart, Lung, and Blood Institute, Bethesda, MD, USA, <sup>4</sup>The Jackson Laboratory, Bar Harbor, ME, USA, <sup>5</sup>Alström Syndrome International, Mt Desert, ME, USA
6. **Hearing Loss and Otologic Outcomes in Fibrous Dysplasia**  
Alison M Boyce<sup>1,2</sup>, Carmen Brewer<sup>3</sup>, Timothy R DeKlotz<sup>4</sup>, Christopher Zalewski<sup>3</sup>, Kelly King<sup>3</sup>, Michael T Collins<sup>1</sup>, H Jeffrey Kim<sup>3,4</sup>  
<sup>1</sup>Section on Skeletal Disorders and Mineral Homeostasis, Craniofacial and Skeletal Diseases Branch, National Institute of Dental and Craniofacial Research, NIH, <sup>2</sup>Bone Health Program, Division of Orthopaedics & Division of Endocrinology and Diabetes, Children's National Health System, <sup>3</sup>Otolaryngology Branch, National Institute on Deafness and Other Communication Disorders, NIH, <sup>4</sup>Department of Otolaryngology-Head & Neck Surgery, Georgetown University Hospital
7. **Finding the Needle in the Haystack: The Use of Whole Exome Sequencing in Determining the Pathogenic Mutations in Patients with Retinal Degeneration**  
Laura Bryant, Olga Lozynska and Jean Bennett  
University of Pennsylvania, Philadelphia, PA
8. **Chronic Hepatocellular Injury in Urea Cycle Disorders**  
Lindsay C. Burrage<sup>1</sup>, Danielle Guffey<sup>2</sup>, Charles G. Minard<sup>2</sup>, Brendan H. Lee<sup>1</sup>, Members of the Urea Cycle Disorders Consortium, Sandesh Nagamani<sup>1</sup>  
<sup>1</sup>Department of Molecular and Human Genetics, Baylor College of Medicine, <sup>2</sup>Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine

---

## Abstract Poster Numbers

- 9. Preliminary Results from a Phase II study of nivolumab (anti-PD-1 antibody) for patients with metastatic adrenocortical carcinoma (ACC)**  
Ludimila Cavalcante<sup>1</sup> MD, Benedito Carneiro<sup>1</sup> MD, Ricardo Costa<sup>1</sup> MD, Alfred Rademaker<sup>1</sup> PhD, Francis Giles<sup>1</sup> MD  
<sup>1</sup> Northwestern University
- 10. Accumulation of globotriaosylceramide (GL3) in cardiomyocytes (CM) is progressive with age and inversely correlates with baseline alpha galactosidase A (AGALA) activity in enzyme replacement therapy (ERT)-naïve Fabry patients with IVS4 + 919G>A mutation**  
Fu-Pang Chang<sup>a,b</sup>, Ting-Rong Hsu<sup>a</sup>, Seng-Che Hung<sup>a</sup>, Shih-Hsien Sung<sup>a</sup>, Wen-Chung Yu<sup>a</sup>, Dau-Ming Niu<sup>a</sup>, Behzad Najafian<sup>b</sup>  
<sup>a</sup>Taipei Veterans General Hospital, Taipei, Taiwan; <sup>b</sup>University of Washington, Seattle, United States
- 11. Cellular Localization and Cl<sup>-</sup>/H<sup>+</sup> Coupling Properties of wild type CIC-5 and patient-specific mutants**  
Min-Hwang Chang<sup>1,3</sup>, Matthew Brown<sup>1,5</sup>, Yiran Liu<sup>2,6</sup>, Vladimir G. Gainullin<sup>2,4</sup>, Peter C. Harris<sup>2,4</sup>, Michael F. Romero<sup>1,3,4</sup>, John C. Lieske<sup>1,3,4</sup>  
<sup>1</sup>Physiology & Biomedical Engineering, <sup>2</sup>Biochemistry and Molecular Biology, <sup>3</sup>O'Brien Urology Research Center; <sup>4</sup>Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN <sup>5</sup>Wayne State University, Detroit, Michigan, USA, <sup>6</sup>University of Michigan, Ann Arbor, MI
- 12. Acute Intermittent Porphyria: Low Penetrance of the Autosomal Dominant Disease Indicates a Significant Role of Genetic Modifiers in Disease Pathogenesis**  
Brenden Chen, Constanza Solis-Villa, Jörg Hakenberg, Wanqiong Qiao, Ramakrishnan R. Srinivasan, Makiko Yasuda, Manisha Balwani, Dana Doheny, Inga Peter, Rong Chen, Robert J. Desnick  
Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY
- 13. Impact of dietary intake on bone turnover in patients with phenylalanine hydroxylase deficiency**  
Kathryn E Coakley<sup>1</sup>, Eric I Felner<sup>2</sup>, Vin Tangpricha<sup>3</sup>, Peter W Wilson<sup>4</sup>, Rani H Singh<sup>5</sup>  
<sup>1</sup>Nutrition and Health Science Program, Laney Graduate School, Emory University, Atlanta, GA, <sup>2</sup>Associate Professor of Pediatrics, Division of Pediatric Endocrinology, Emory University School of Medicine, Atlanta, GA, <sup>3</sup>Associate Professor, Division of Endocrinology, Metabolism and Lipids, Emory University School of Medicine, Atlanta VA Medical Center, Atlanta, GA, <sup>4</sup>Clinical Cardiovascular Research Institute, School of Medicine, Emory University, Atlanta, GA, <sup>5</sup>Metabolic Nutrition Program, Department of Human Genetics, School of Medicine, Emory University, Atlanta, GA
- 14.  $\beta$ -Cyclodextrin Polyrotaxanes as Potential Niemann-Pick Type C Therapeutics: From Design to In Vivo Therapeutic Efficacy**  
C. J. Collins<sup>1</sup>, Y. Mondjinou<sup>1</sup>, S. Alam<sup>2</sup>, B. Loren<sup>1</sup>, K. Halder<sup>2</sup>, D. H. Thompson<sup>1</sup>  
<sup>1</sup>Purdue University. West Lafayette, IN 47906. <sup>2</sup>University of Notre Dame. Notre Dame, IN 46556.
- 15. Idiopathic Bronchiectasis and Heritable Connective Tissue Disorders: A Reflection of Shared Genetic Variation**  
M. Leigh Anne Daniels MD, MPH; Maimoona A Zariwala PhD; Michael R. Knowles MD  
University of North Carolina, Chapel Hill, NC
- 16. Correlation of chest CT findings to spirometry in children with primary ciliary dyskinesia**  
Ashley Deschamp<sup>1</sup>, Matthew Cooper<sup>2</sup>, Brandon Brown<sup>2</sup>, Mark Baskin<sup>2</sup>, Sarah Kleiman<sup>1</sup>, Thomas Ferkol<sup>3</sup>, Margaret Rosenfeld<sup>4</sup>, Hye-Seung Lee<sup>5</sup>, Sharon Dell<sup>6</sup>, Scott Sagel<sup>7</sup>, Carlos Milla<sup>8</sup>, Michael Knowles<sup>9</sup>, Margaret Leigh<sup>10</sup>, Stephanie Davis<sup>1</sup>.  
<sup>1</sup>Department of Pediatrics and <sup>2</sup>Radiology, Indiana University School of Medicine; <sup>3</sup>Department of Pediatrics, Washington University School of Medicine; <sup>4</sup>Department of Pediatrics, University of Washington; <sup>5</sup>Department of Pediatrics, University of South Florida; <sup>6</sup>Department of Pediatrics, University of Toronto; <sup>7</sup>Department of Pediatrics, University of Colorado School of Medicine; <sup>8</sup>Department of Pediatrics, Stanford University; <sup>9</sup>Department of Medicine and <sup>10</sup>Pediatrics, University of North Carolina School of Medicine.
- 17. Defining Hand Stereotypies in Rett Syndrome: A Movement Disorders Perspective**  
Marisela E. Dy<sup>1,2</sup>, Jeff L. Waugh<sup>1,2</sup>, Nutan Sharma<sup>1,2</sup>, Heather O'Leary<sup>1</sup>, Kush Kapur<sup>1</sup>, Alissa D' Gama<sup>3</sup>, Mustafa Sahin<sup>1</sup>, David K. Urion<sup>1</sup>, Walter E. Kaufmann<sup>1</sup>  
<sup>1</sup>Boston Children's Hospital, <sup>2</sup>Massachusetts General Hospital, <sup>3</sup>Harvard Medical School

**18. Implications of Glycolate Metabolism on Mitochondria in Primary Hyperoxaluria**

Sonia Fargue<sup>1</sup>, Tanecia Mitchell<sup>1</sup>, John Knight<sup>1</sup>, Ross P. Holmes<sup>1</sup>

<sup>1</sup> University of Alabama at Birmingham. Department of Urology, Birmingham, AL.

**19. Phenotypic Characteristics of Phelan-McDermid Syndrome from the Phelan-McDermid Syndrome International Registry**

Cristan Farmer<sup>1</sup>, Audrey Thurm<sup>1</sup>, Jill Leon<sup>1</sup>, Latha Soorya<sup>2</sup>, Megan O'Boyle<sup>3</sup>, Rebecca Davis<sup>3</sup>, & Paul Avillach<sup>4</sup>

<sup>1</sup>National Institute of Mental Health, <sup>2</sup>Rush University Medical Center, <sup>3</sup>Phelan-McDermid Syndrome Foundation, <sup>4</sup>Harvard Medical School

**20. Clinical Presentations of Relapsing Polychondritis: More Than a Swollen Ear**

<sup>1,2,3</sup>Marcela A. Ferrada, M.D., <sup>2</sup>Ninet Sinai PhD, MPH <sup>3</sup>Shubhasree Choudhury MD, Thomas Christie<sup>4</sup> and

<sup>3</sup>James D. Katz, M.D

<sup>1</sup>Critical Care Department National Institutes of Health, Bethesda, MD, <sup>2</sup>National Institutes of Health Clinical Center, Bethesda, MD, <sup>3</sup>National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD <sup>4</sup>Relapsing Polychondritis Awareness and Support Foundation

**21. Characterizing Sleep in Rett Syndrome Using Actigraphy**

Alyssa M. Merbler<sup>1</sup>, Breanne J. Byiers<sup>1</sup>, John J. Garcia<sup>2</sup>, Timothy J. Feyma<sup>2</sup>, & Frank J. Symons<sup>1</sup>

<sup>1</sup>Department of Educational Psychology, University of Minnesota, Minneapolis, MN <sup>2</sup>Gillette Children's Specialty Healthcare, St. Paul, MN

**22. Gluteus Maximus Activation during Ambulation in Children with Osteogenesis Imperfecta (OI)**

<sup>1</sup>Jessica Fritz, <sup>2</sup>Peter Smith & <sup>1,2</sup>Gerald Harris

<sup>1</sup>Marquette University/Medical College of Wisconsin, Milwaukee, WI; <sup>2</sup>Shriners Hospitals for Children, Chicago, IL

**23. Gait Deviations in Children with Osteogenesis Imperfecta**

Christina Garman<sup>1</sup> Adam Graf<sup>2</sup>, Joseph Krzak<sup>2</sup>, Angela Caudill<sup>2</sup>, Peter Smith<sup>2</sup>, and Gerald Harris<sup>1,2</sup>

<sup>1</sup>Marquette University, Milwaukee WI, <sup>2</sup>Shriners Hospitals for Children Chicago, Chicago IL

**24. Pulmonary radio-aerosol mucociliary scan to evaluate Primary ciliary dyskinesia in children with bronchiectasis**

Hasan Ghandourah, Reza Vali, , Kimia Veisi nezhad , Yusauf Omerkheil , Afsoon Khazaei, Martin Charron, Amer Shammam and Sharon Dell

Departments of Pediatric Respiratory Medicine, Medical Imaging and Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada. Brampton nuclear service, Brampton, Ontario, Canada.

**25. Variation in erythrocyte and plasma protoporphyrin levels over time in protoporphyrias**

Gou E<sup>1</sup> , Weng C<sup>2</sup>, Phillips JD<sup>2</sup>, Greene T<sup>2</sup>, Balwani M<sup>3</sup>, Bissell DM<sup>4</sup>, Bloomer JR<sup>5</sup>, Bonkovsky HL<sup>6</sup>, Desnick RJ<sup>3</sup>, Naik H<sup>3</sup>, Sadagoparamanujam VM<sup>1</sup>, Anderson KE<sup>1</sup>

<sup>1</sup>U of Texas Medical Branch, Galveston TX; <sup>2</sup>U of Utah, Salt Lake City, UT; <sup>3</sup>Icahn S of Med at Mt. Sinai, NY, NY;

<sup>4</sup>U of CA at San Francisco; <sup>5</sup>U of AL at Birmingham; and <sup>6</sup>Wake Forest University, Winston-Salem, NC

**26. MEP1A mutation identified by whole exome sequencing in a family with slipped capital femoral epiphysis**

Yiran Guo<sup>1</sup>, Hakon Hakonarson<sup>1,2,3</sup>.

1) Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; 2) Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; 3) Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.

**27. The NHLBI Lymphangioma Registry-Longitudinal Analysis of Pulmonary Function**

N. Gupta<sup>1</sup>, H.S. Lee<sup>2</sup>, J. Moss<sup>3</sup>, A.M. Taveira-DaSilva<sup>3</sup>, G.J. Beck<sup>4</sup>, J.H. Ryu<sup>5</sup>, F. X. McCormack<sup>1</sup> and the NHLBI LAM Registry Group.

<sup>1</sup> University of Cincinnati, Cincinnati-OH; <sup>2</sup> University of South Florida, Tampa-FL <sup>3</sup>National Heart, Lung, and Blood Institute, Bethesda-MD; <sup>4</sup> Cleveland Clinic Foundation, Cleveland-OH; <sup>5</sup> Mayo Clinic, Rochester-MN

---

## Abstract Poster Numbers

- 28. Initial Presentation of Dyskeratosis Congenita in IFIH1 Mutations With an Associated Phenotype of Aicardi Goutieres Syndrome**  
S Hamoud, K Marathe, A Vanderver, S. Hufnagel, K.A. Chapman  
Children's National Health System, Washington DC
- 29. PKAN (Pantothenate Kinase 2-Associated Neurodegeneration) Mouse Models Showed Changes Resembling Human Patients; A New Chance for Pre-Clinical Trials**  
Suh Young Jeong, PhD, Jeffrey Hamada, BA, Rachel Fox, BA, Martina Ralle, PhD, Suzanne Mitchell, PhD, Penelope Hogarth, MD, and Susan J. Hayflick, MD.  
Oregon Health and Science University, Portland, OR, USA
- 30. Assessing the Driving Ability in Those with Charcot Marie Tooth Disease Type 1A (CMT1A)**  
Jerath, N. et al.  
Inherited Neuropathies Consortium, University of Iowa Carver College of Medicine, Iowa City, IA
- 31. Role of Oxidative Stress and Inflammation in Type 1 Gaucher Disease (GD1): Potential Use of Antioxidant/Anti-inflammatory Medications**  
Reena V. Kartha<sup>1</sup>, Ghada Elnashar<sup>1</sup>, James Joers<sup>2</sup>, Paul Tuite<sup>3</sup>, Laurie Hovde<sup>1</sup>, Usha Mishra<sup>1</sup>, Kyle Rudser<sup>4</sup>, Gulin Oz<sup>2</sup>, Jeanine James Utz<sup>1,5</sup>, James Cloyd<sup>1</sup>  
<sup>1</sup>Center for Orphan Drug Research, <sup>2</sup>Center for Magnetic Resonance Research; <sup>3</sup>Neurology; <sup>4</sup>Biostatistics; University of Minnesota; <sup>5</sup>UMN Medical Center/Fairview Health Systems, Minneapolis, Minnesota, United States, 55455
- 32. A Multicenter North American Study of the Gillette FAQ in Osteogenesis Imperfecta**  
Kruger KM<sup>1</sup>, Caudill A<sup>2</sup>, Nagamani CS<sup>3</sup>, Smith PA<sup>2</sup>, Harris GF<sup>1,2</sup>, Members of the BBD Consortium\*  
<sup>1</sup>Marquette University, Milwaukee, WI, <sup>2</sup>Shriners Hospitals for Children, Chicago, IL, <sup>3</sup>Baylor College of Medicine, Houston, TX
- 33. A Prospective, Multicenter Study to Compare and Validate Endoscopic, Histologic, Molecular, and Patient-Reported Outcomes in Patients with Eosinophilic Gastro-intestinal Diseases**  
Rothenberg ME<sup>1</sup>, Kuhl JT<sup>1</sup>, Aceves SS<sup>1</sup>, Carpenter C<sup>1</sup>, Dellon ES<sup>1</sup>, Falk GW<sup>1</sup>, Gonsalves NP<sup>1</sup>, Gupta SK<sup>1</sup>, Hirano I<sup>1</sup>, Kantor S<sup>1</sup>, Leung J<sup>1</sup>, Spergel JM<sup>1</sup>, Wershil BK<sup>1</sup>, Venter C<sup>1</sup>, Furuta GT<sup>1</sup>,  
<sup>1</sup>Consortium of Eosinophilic Gastrointestinal Researchers
- 34. The impact of the disease burden on the quality of life of patients with lysosomal storage disorders: preliminary data of adult patients**  
Sandra Obikawa Kyosen, Erika Mitie Yamashiro Coelho, Kelin Chen, Edna Tiemi Sakata, Rosangela Maria da Silva, Ana Maria Martins  
Reference Center of Inborn Errors of Metabolism, Federal University of Sao Paulo
- 35. Evidence of multiple carboxylase deficiency in children with mutations in *MT-ATP6***  
Austin A. Larson<sup>1</sup>, Shanti Balasubramaniam<sup>2</sup>, John Christodoulou<sup>3</sup>, George A. Diaz<sup>4</sup>, Emma Glamuzina<sup>5</sup>, Natalie Hauser<sup>6</sup>, Bryce Heese<sup>7</sup>, Gabriella Horvath<sup>8</sup>, Andre Mattman<sup>8</sup>, S. Lane Rutledge<sup>10</sup>, Clara Van Karnebeek<sup>8</sup>, Amy Williamson<sup>4</sup>, Johan K. L. Van Hove<sup>1</sup>, James D. Weisfeld-Adams<sup>1</sup>  
<sup>1</sup>University of Colorado School of Medicine, Aurora, CO; <sup>2</sup>Princess Margaret Hospital, Perth, Australia; <sup>3</sup>University of Melbourne, Melbourne, Australia; <sup>4</sup>Icahn School of Medicine at Mount Sinai, New York, NY; <sup>5</sup>Starship Children's Hospital, Auckland, New Zealand; <sup>6</sup>Valley Children's Hospital, Madera, CA; <sup>7</sup>University of Missouri-Kansas City School of Medicine, Kansas City, MO; <sup>8</sup>University of British Columbia, Vancouver, Canada; <sup>9</sup>University of Alabama at Birmingham, Birmingham, AL
- 36. Diagnostic Delays in Rare Disease: Identifying Factors and Developing Strategies to Address**  
Latino GA, Kim H, McCulloch C, Faughnan ME, and the Brain Vascular Malformation Consortium HHT Investigator Group  
1) Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada, 2) Division of Respiriology and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada, 3) Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, University of California, San Francisco, USA, 4) Institute for Human Genetics, University of California, San Francisco, USA

**37. Whole exome sequencing identifies genes converge on PI3K/mTOR and Ras/MAPK pathways as causes of generalized lymphatic anomaly**

Dong Li<sup>1</sup>, Tara L. Wenger<sup>2</sup>, Michael March<sup>1</sup>, Christoph Seiler<sup>3</sup>, Alvaro Gutierrez-Uzquiza<sup>1</sup>, Lifeng Tian<sup>1</sup>, Charly Kao<sup>1</sup>, Rahul Pandey<sup>1</sup>, Kenny Nguyen<sup>1</sup>, Rosetta Chiavacci<sup>1</sup>, Patrick Sleiman<sup>1,4</sup>, Maxim Itkin<sup>5</sup>, Yoav Dori<sup>5</sup>, Hakon Hakonarson<sup>1,4,6</sup>

1. Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA, 2. Division of Craniofacial Medicine, Seattle Children's Hospital, Seattle, WA, 3. Zebrafish core, The Children's Hospital of Philadelphia, Philadelphia, PA, 4. Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, 5. Center for Lymphatic Imaging and Interventions, The Children's Hospital of Philadelphia, Philadelphia, PA, 6. Divisions of Genetics and Pulmonary Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA

*\*Abstract selected for an oral presentation. There will be no poster.*

**38. Persistent transaminitis and dyslipidemia in a boy due to lysosomal acid lipase deficiency and response to enzyme replacement therapy.**

Mari Mori, Basavaraj M Kerur, Neal LeLeiko, Chanika Phornphutkul

Hasbro Children's Hospital, The Warren Alpert Medical School of Brown University, Providence, RI

**39. Esophageal Distensibility Provides Measure of Remodeling in Pediatric Eosinophilic Esophagitis**

Amanda Muir<sup>1</sup>, Alain Benitez<sup>1</sup>, Ritu Verma<sup>1</sup>, Chris Liacouras<sup>1</sup>, Robert Kramer<sup>2</sup>, Jonathan Spergel<sup>1</sup>, Glenn Furuta<sup>2</sup>, Calies Menard-Katcher<sup>2</sup>

<sup>1</sup>The Children's Hospital of Philadelphia, <sup>2</sup>Children's Hospital Colorado

**40. Nutrient intake in children with Smith-Lemli-Opitz syndrome**

Semone B. Myrie<sup>1</sup>, Kate Haas<sup>2</sup>, Forbes D. Porter<sup>3</sup>, James Heubi<sup>4</sup>, Robert D. Steiner<sup>5</sup>, Peter H. Jones<sup>1</sup>, Jean-Baptiste Roullet<sup>2,6</sup>

<sup>1</sup>University of Manitoba, Winnipeg, MB, Canada, <sup>2</sup>Oregon Health & Science University, Portland, OR, USA; <sup>3</sup>The Eunice Kennedy Shriver National Institute of Child Health & Development, Bethesda, MD, USA; <sup>4</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; <sup>5</sup>University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; <sup>6</sup>College of Pharmacy, Washington State University, Spokane, WA, USA.

**41. FVII deficiency: Studies of the Natural History, Genotype-Phenotype Correlations, and Opportunities for Therapeutic Intervention.**

Danielle Nance, MD, Arizona Bleeding Disorders Health and Wellness Center

**42. Descriptive analysis of gut microbiome alterations in hyperoxaluric patients**

Lama Nazzal<sup>1</sup>, David S. Goldfarb<sup>1</sup>, John Lieske<sup>2</sup>, Dawn Milliner<sup>2</sup>, Martin Blaser<sup>1</sup>.

1. New York University School of Medicine, New York, 2. Mayo Clinics, Rochester, Minnesota.

**43. Extra-Pulmonary Morbidity in a Rare Lung Disease: Growth and Developmental Impacts in Neuroendocrine Cell Hyperplasia of Infancy (NEHI)**

Rebekah J. Nevel, Errine Garnett, Abigail Arkon, Na Liu, and Lisa R. Young

Division of Pediatric Pulmonary Medicine, Vanderbilt University Medical Center

**44. Characterization of Idiopathic Bronchiectasis in Patients with and without Pulmonary Nontuberculous Mycobacterial Disease**

J.A. Nguyen,<sup>1</sup> D.R. Prevots,<sup>2</sup> J. Adjemian,<sup>2,3</sup> Y. Lai,<sup>2</sup> C.M. Henderson,<sup>4</sup> M.L.A. Daniels,<sup>5</sup> M.R. Knowles,<sup>5</sup> C. L. Daley,<sup>6</sup> K.N. Olivier<sup>1</sup>

<sup>1</sup>National Heart, Lung, and Blood Institute - Bethesda, MD/US, <sup>2</sup>National Institute of Allergy and Infectious Diseases - Bethesda, <sup>3</sup>United States Public Health Service, Commissioned Corps - Rockville, MD/US, <sup>4</sup>National Institutes of Health Clinical Center - Bethesda, MD/US, <sup>5</sup>University of North Carolina - Chapel Hill/US, <sup>6</sup>National Jewish Health - Denver/US; Genetic Diseases of Mucociliary Clearance Consortium

**45. Psychosocial predictors of depression in people with mast cell disorders**

Jennifer Nicoloso-SantaBarbara<sup>1</sup>, Marci Lobel<sup>1</sup>, David Wolfe<sup>2</sup>

<sup>1</sup> Department of Psychology, Stony Brook University, Stony Brook, New York, USA, <sup>2</sup> Division of Medical Psychiatry, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

---

## Abstract Poster Numbers

- 46. ZFN-mediated liver-targeting gene therapy corrects systemic and neurological diseases of mucopolysaccharidosis type I**  
Li Ou<sup>1</sup>, Russell DeKever<sup>2</sup>, Susan Tom<sup>2</sup>, Robert Radeke<sup>2</sup>, Michelle Rohde<sup>2</sup>, Amy Manning-Bog<sup>2</sup>, Scott Sproul<sup>2</sup>, Michael J Przybilla<sup>3</sup>, Brenda L Koniar<sup>1</sup>, Kelly Podetz-Pedersen<sup>3</sup>, Kanut Laoharawee<sup>3</sup>, Renee D Cooksley<sup>1</sup>, Michael C Holmes<sup>2</sup>, Thomas Wechsler<sup>2</sup>, R Scott McIvor<sup>3</sup>, Chester B Whitley<sup>1</sup>  
<sup>1</sup>Gene Therapy Center, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, <sup>2</sup> Sangamo BioSciences, Inc. 501 Canal Boulevard, Richmond, CA 94804, <sup>3</sup> Department of Genetics, Cell Biology and Development, University of Minnesota, Minneapolis, Minnesota.
- 47. Defining disease subtypes in pediatric pulmonary hypertension: A network approach**  
Mei-Sing Ong, Kenneth Mandl  
Boston Children's Hospital, Harvard Medical School  
*\*Abstract selected for an oral presentation. There will be no poster.*
- 48. Improvements in Spina Bifida Associated Infant Mortality**  
Nelson D. Pace, David J. Wilde  
Department of Epidemiology, University of North Carolina at Chapel Hill (NDP), School of Medicine, University of Texas Health Sciences Center at San Antonio (DJW)
- 49. Neuropsychological profile in Sjögren's syndrome.**  
Pérez Martínez, Sara.  
Complutense University of Madrid (Spain). Department of Basic Psychology, Quaes Foundation (Valencia, Spain)
- 50. Cortical excitability is not different between healthy controls and people with laryngeal dystonia**  
Cecilia N. Prudente<sup>1</sup>, Mo Chen<sup>1</sup>, Rebekah L. Schmidt<sup>1</sup>, George S. Goding<sup>2</sup>, Sharyl Samargia<sup>3</sup>, Christy L. Ludlow<sup>4</sup>, Teresa J. Kimberley<sup>1</sup>  
1. Department of Rehabilitation Medicine, University of Minnesota, 2. Department of Otolaryngology, Head and Neck Surgery, University of Minnesota, 3. Department of Communication Sciences and Disorders, University of Wisconsin River Falls, 4. Department of Communication Sciences and Disorders, James Madison University
- 51. Helping Patients to Navigate the Clinical-Research Divide**  
Kimberly Splinter<sup>1</sup>, Matthew Might<sup>1,2</sup>, Cecilia Esteves<sup>1</sup>, Isaac Kohane<sup>1</sup>, Rachel Ramoni<sup>1,3</sup>  
<sup>1</sup>Department of Biomedical Informatics, Harvard Medical School, <sup>2</sup>School of Computing, University of Utah, <sup>3</sup>Department of Epidemiology and Health Promotion, New York University College of Dentistry
- 52. Development of a Pregnancy Self-Report Survey for Osteogenesis Imperfecta**  
Rashmi Rao MD<sup>1</sup>, Deborah Krakow MD<sup>2</sup>.  
<sup>1</sup> University of California, Los Angeles Department of Obstetrics and Gynecology. <sup>2</sup> University of California, Los Angeles Department of Orthopaedic Surgery
- 53. Validation of a Diary Score for Assessment of Symptom Pattern and Treatment Response in Sting-Associated Vasculopathy with Onset in Infancy (SAVI) and Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature (CANDLE)**  
Megha Sawhney<sup>1</sup>, Gina Montealegre<sup>2</sup>, Robert Wesley<sup>3</sup>, Kost Bahar<sup>1</sup>, Raphaela Goldbach-Mansky<sup>2</sup>  
<sup>1</sup>Rheumatology Fellowship Program, National Institutes of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), <sup>2</sup>Translational Autoinflammatory Disease Studies, National Institute of Allergy and Infectious Diseases (NIAID), <sup>3</sup>Clinical Center, NIH
- 54. Scarless gene correction of arginase-1 deficiency in mouse iPSCs using CRISPR/Cas9-mediated gene targeting and *piggyBac* transposase**  
Yuan Yan Sin, Phillipe Price, Laurel Ballantyne, Crystal McCracken, Colin D. Funk  
Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON K7L 3N6 Canada

**55. Specific targeting of E3s augments CFTR correction and function.**

Riling, Christopher<sup>1</sup>; Sterner, David<sup>1</sup>; Wu, Jian<sup>1</sup>; Sokirniy, Ivan<sup>1</sup>; Chung, Wook Joon<sup>2,3</sup>; Fortenberry, James<sup>2</sup>; Zhang, Zairong<sup>1</sup>; Butt, Tauseef<sup>1</sup>; Chiang, Annette<sup>4</sup>; Goeckeler-Fried, Jennifer<sup>4</sup>; Brodsky, Jeffrey<sup>4</sup>; Sorscher, Eric J.<sup>2,5</sup>; Mattern, Michael<sup>1</sup>; Kumar, Suresh<sup>1</sup>

1. Progenra Inc, Malvern, PA, USA, 2. Cystic Fibrosis Research Center, Univ of Alabama at Birmingham, Birmingham, AL, USA, 3. Neurobiology, Univ of Alabama at Birmingham, Birmingham, AL, USA, 4. Biological Sciences, Univ of Pittsburgh, Pittsburgh, PA, USA, 5. Medicine, Univ of Alabama at Birmingham, Birmingham, AL, USA

**56. Endocytic alterations in Lysosomal Storage Diseases human brains**

Melani A. Solomon<sup>1</sup>, Ronaldo Moscoso<sup>1</sup>, Ronelle Bautista<sup>2</sup>, Silvia Muro<sup>1,2</sup>

<sup>1</sup>Institute of Bioscience and Biotechnology Research, University of Maryland, College Park, USA, <sup>2</sup>Fischell Department of Bioengineering, University of Maryland, College Park, USA

**57. Volumetric Analysis of the Basal Ganglia in Patients with Phelan-McDermid Syndrome**

Siddharth Srivastava<sup>1</sup>, Anna Prohl<sup>2</sup>, Benoit Scherrer<sup>2</sup>, Simon K. Warfield<sup>2</sup>, Mustafa Sahin<sup>1</sup>

<sup>1</sup>Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA,

<sup>2</sup>Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA

**58. Double Support Times During Treadmill Walking Are Associated With MECP2 Mutation Type In Rett Syndrome**

Bernhard Suter<sup>1</sup>, David Young<sup>2,3</sup>, Beom-Chan Lee<sup>2,3</sup>, Daniel G. Glaze<sup>1</sup>, Charles S. Layne<sup>2,3</sup>

<sup>1</sup>Blue Bird Circle Rett Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, <sup>2</sup>Center for Neuromotor and Biomechanics Research, <sup>3</sup>Department of Health and Human Performance, University of Houston, Houston, TX

**59. Surgical Outcomes for Brain Arteriovenous Malformation Resection in Patients with Hereditary Hemorrhagic Telangiectasia**

Ali Tayebi Meybodi, MD<sup>1</sup>, Helen Kim, PhD<sup>2,4</sup>, Jeffrey Nelson, MS<sup>2,4</sup>, Steven W. Hetts, MD<sup>3,4</sup>, Timo Krings, MD<sup>5</sup>, Karel G. terBrugge<sup>5</sup>, Marie E. Faughnan, MD, MSc<sup>6</sup>, Michael T. Lawton, MD<sup>1,2,4</sup>, and the Brain Vascular Malformations Consortium HHT Investigator Group<sup>‡</sup>,

<sup>1</sup>Department of Neurological Surgery, University of California, San Francisco, <sup>2</sup>Department of Anesthesia and Perioperative Care, University of California, San Francisco, <sup>3</sup>Division of Neurointerventional Radiology, Department of Radiology and Biomedical Imaging, University of California, San Francisco, <sup>4</sup>Center for Cerebrovascular Research, University of California, San Francisco, <sup>5</sup>Division of Neuroradiology, Department of Medical Imaging, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada, <sup>6</sup>Division of Respiratory, Keenan Research centre, and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada. <sup>‡</sup> Brain Vascular Malformation Consortium HHT Investigator Group: Murali Chakinala, Marianne Clancy, Marie E. Faughnan, James R. Gossage, Katharine Henderson, Steven Hetts, Vivek Iyer, Raj Kasthuri, Helen Kim, Timo Krings, Michael T. Lawton, Doris Lin, Johannes Jurgen Mager, Charles E. McCulloch, Justin McWilliams, Jamie McDonald, Ludmila Pawlikowska, Jeffrey Pollak, Felix Ratjen, Karen Swanson, Karel terBrugge, Dilini Vethanayagam, Andrew White, Robert I. White Jr, Pearce Wilcox

**60. Longitudinal Trends in Respiratory Microbiology and Pulmonary Function in Primary Ciliary Dyskinesia: Comparisons to a Cystic Fibrosis Cohort**

M.C. Tracy, J.M. Zirbes, C. Hernandez, C.E. Milla

Stanford University School of Medicine, Palo Alto, CA/US

**61. Atypical Femur Fractures in Osteogenesis Imperfecta**

Pamela Trejo, Francis H. Glorieux and Frank Rauch.

Shriners Hospital for Children Canada and McGill University

**62. In-depth characterization of patients with repeat expansions in C9ORF72**

Marka van Blitterswijk<sup>1</sup>, NiCole A. Finch<sup>1</sup>, Mariely DeJesus-Hernandez<sup>1</sup>, Tania F. Gendron<sup>1</sup>, Keith A. Josephs<sup>2</sup>, Joseph E. Parisi<sup>2</sup>, David S. Knopman<sup>2</sup>, Ronald C. Petersen<sup>2</sup>, Bradley F. Boeve<sup>2</sup>, Neill R. Graff-Radford<sup>3</sup>, Leonard Petrucelli<sup>1</sup>, Dennis W. Dickson<sup>1</sup>, Kevin B. Boylan<sup>3</sup> and Rosa Rademakers<sup>1</sup>

<sup>1</sup>Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL, <sup>2</sup>Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN, and <sup>3</sup>Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL

---

## Abstract Poster Numbers

**63. A Prospective, Multicenter Study of Differential Clinical Characteristics of Adults and Children with Eosinophilic Gastrointestinal Diseases (OMEGA)**

Venter C<sup>1</sup>, Furuta GT<sup>1</sup>, Aceves SS<sup>1</sup>, , Carpenter C<sup>1</sup>, Dellon ES<sup>1</sup>, Falk GW<sup>1</sup>, Gonsalves NP<sup>1</sup>, Gupta SK<sup>1</sup>, Hirano I<sup>1</sup>, Kantor S<sup>1</sup>, Leung J<sup>1</sup>, Spergel JM<sup>1</sup>, Wershil BK<sup>1</sup>, Kuhl JT<sup>1</sup>, Rothenberg ME<sup>1</sup>

<sup>1</sup> Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)

**64. Determining the natural history of Alexander disease: a pilot study**

Waldman AT<sup>1</sup>, Liu G<sup>1</sup>, Lavery A<sup>1</sup>, Messing A<sup>2</sup>, Vanderver A<sup>1</sup>.

<sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, <sup>2</sup>University of Wisconsin-Madison, Madison, WI

**65. A Novel Statistic for Assessing Inter-Pathologist Agreement in the Nephrotic Syndrome Study Network (NEPTUNE) Kidney Biopsy Evaluation**

Jarcy Zee<sup>1</sup>, Laura Mariani<sup>1,2</sup>, Jeffrey Hodgin<sup>2</sup>, Joseph Gaut<sup>3</sup>, Matthew Palmer<sup>4</sup>, Lawrence Holzman<sup>4</sup>, Laura Barisoni<sup>5</sup>, Brenda Gillespie<sup>2</sup>. <sup>1</sup>Arbor Research Collaborative for Health, Ann Arbor, MI; <sup>2</sup>University of Michigan, Ann Arbor, MI; <sup>3</sup>Washington University, St. Louis, MO; <sup>4</sup>University of Pennsylvania, Philadelphia, PA; <sup>5</sup>University of Miami, Miami, FL



## Rare Diseases Clinical Research Network Summaries

### 66. CPAG: The Power of Coalition

Coalition of Patient Advocacy Groups

### 67. Data Management and Coordinating Center Summary

Principal Investigator: Jeffrey Krischer, PhD

### 68. Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) Clinical Research Consortium

Principal Investigators: Adam L. Boxer, MD, PhD. and Howard J. Rosen, MD

### 69. Autonomic Disorders Consortium

Principal Investigator: David Robertson, MD – Vanderbilt University

### 70. Brain Vascular Malformation Consortium

Principal Investigator: Michael T. Lawton, MD; Co-PI: Douglas A. Marchuk, PhD

### 71. Brittle Bone Disorders Consortium

Principal Investigator: Brendan Lee, MD, PhD

### 72. Consortium of Eosinophilic Gastrointestinal Disease Researchers

Principal Investigator: Marc Rothenberg, MD, PhD

### 73. Clinical Research in ALS and related disorders for Therapy development Consortium

Principal Investigator: Michael Benatar, MD, PhD

### 74. Developmental Synaptopathies Consortium

Principal Investigator: Mustafa Sahin, MD, PhD

### 75. Dystonia Coalition

Principal Investigator: Hyder A. Jinnah, M.D., PhD

### 76. Genetic Disorders of Mucociliary Clearance Consortium

Principal Investigator: Michael R Knowles, MD

### 77. Inherited Neuropathies Consortium

Principal Investigator: Michael Shy, MD

### 78. Lysosomal Disease Network (LDN)

Principal Investigator: Chester Whitley, MD, PhD; James C. Cloyd, PharmD; Administrative Director

### 79. NEPTUNE; Nephrotic Syndrome Study Network

Principal Investigator: Matthias Kretzler, MD

### 80. Nephrotic Syndrome Study Network (NEPTUNE) Training Program in Clinical and Translational Research in Human Glomerular Disease

Matthias Kretzler<sup>1</sup>, Larry Holzman<sup>2</sup>, The NEPTUNE Consortium, [Tina Mainieri](#)<sup>1</sup>

### 81. North American Mitochondrial Disease Consortium (NAMDC)

Principal Investigator: Dr. Michio Hirano, MD

### 82. Porphyrias Consortium of the Rare Diseases Clinical Research Network

Principal Investigator: Robert J. Desnick, PhD, MD

### 83. Primary Immune Deficiency Treatment Consortium (PIDTC)

Principal Investigator: Morton J Cowan, M.D.

---

## Abstract Poster Numbers

### **84. Rare Kidney Stone Consortium (RKSC)**

Principal Investigator: Dr. Dawn Milliner, Co-P.I. Dr. John Lieske

### **85. Rare Lung Diseases Consortium**

Principal Investigator: Bruce C. Trapnell, MD

### **86. Rett Syndrome, MECP2 Duplication Disorder, and Rett-related Disorder Consortium**

Principal Investigator: Alan Percy, MD – University of Alabama at Birmingham

Study Administrator and Co-PI: Jeffrey Neul, MD, PhD – University of California San Diego

Project Manager: Jane Lane, RN BSN – University of Alabama at Birmingham

### **87. Sterol and Isoprenoid Research Consortium (STAIR)**

Principal Investigator: William B.Rizzo, M.D.

### **88. Urea Cycle Disorders Consortium (UCDC)**

Principal Investigator: Mendel Tuchman, M.D

### **89. Vasculitis Clinical Research Consortium (VCRC)**

Principal Investigator: Peter A. Merkel, MD, MPH

## 1. Evaluation of acute porphyria (AP) in patients presenting to an Emergency Department (ED) with recurrent/unexplained abdominal pain.

Anupam Aditi, MD, UCSF  
D. Montgomery Bissell, MD, UCSF

**Objective:** Evaluate ED patients meeting a clinical profile suggestive of AP. Test for elevated urine PBG using a rapid qualitative test, with confirmation by a standard quantitative test. In performing above, determine prevalence of AP in this higher-risk population.

**Background:** A diagnosis of AP is often missed because AP is considered rare and distinguishing features of AP are poorly known. A study of 108 patients with AP noted a mean delay in diagnosis of 15 years. Females aged 16-45, many with recurrent attacks, are most likely to present with active porphyria, representing ~80% of acute attacks.

With regard to the number of at risk individuals, a study involving 3350 healthy blood donors found prevalence for AP mutations of 1:1600. Another study evaluated 108 patients with acute polyneuropathy and found that 21% had AP, most were previously undiagnosed. Although limited, such findings suggest that AP should be a diagnostic consideration in the ED more often.

**Methods:** Females, age 16-45, who undergo evaluation in the UCSF ED for abdominal pain of unknown cause will be enrolled. Per standard management, a urine sample on admission will be obtained for all patients. A flow sheet for a possible diagnosis of AP will be available to ED providers. If after the initial work-up, porphyria is suspected, the ED physician will order a urine ALA, PBG and urine creatinine. The ED physician will establish verbally that the patient is willing to be contacted about a possible diagnosis of acute porphyria. The study coordinators will obtain consent and administer the study questionnaire. Following consent, urine leftover from usual care will be procured from the chemistry lab and tested for porphobilinogen (PBG) by a rapid method (e.g., the Watson-Schwartz test). The result will be compared with the standard quantitative test for PBG requested by the ED provider.

**Result:** Roadblocks unique to rare diseases have been encountered in implementation. They include a viewpoint amongst ED physicians that evaluation for porphyria is research rather than standard of care and the inability of chemistry labs to handle a high volume of send-out tests.

**Conclusion:** Although a study protocol has been developed and approved by UCSF IRB, several roadblocks unique to rare diseases have been met in its implementation in the ED setting.

## 2. Near Patient Quantification of Ammonia in Whole Blood Samples

Omar B. Ayyub<sup>1</sup>, Brian T. Heligman<sup>2</sup>, Gary Cunningham<sup>1</sup>, Peter Kofinas<sup>3</sup>, and Marshall Summar<sup>1</sup>

<sup>1</sup>Genetics and Metabolism, Children's National Medical Center, Washington, DC 20010

<sup>2</sup>Material Science and Engineering, University of Maryland, College Park, MD 20740

<sup>3</sup>Fischell Department of Bioengineering, University of Maryland, College Park, MD 20740

**Objective:** Hyperammonemia, a life-threatening condition, is characterized by elevated blood ammonia levels and causes severe neurodevelopmental complications. The condition originates from metabolic disturbances in the urea cycle caused by several different inborn errors of metabolism. Currently the monitoring of ammonia levels has to be performed in a hospital furnished with specialized equipment, necessitating a trip to the hospital each time the patient has an appearance of a crisis. The restriction of testing in hospitals makes disease management difficult as there is no real option for precise control over blood ammonia levels. To provide a means for the rapid, analytical monitoring of blood ammonia, a quantitative point-of-care blood ammonia sensor was engineered utilizing a specific, colorimetric ammonia reaction, in tandem with a cation exchange membrane.

**Methods:** The laboratory prototype test sensor's ability to accurately measure blood ammonia was directly correlated with measurements taken by the Siemens EXL, a clinical chemical analyzer currently used in hospital laboratories around the nation. Blood ammonia samples were split into 40  $\mu$ L and 200  $\mu$ L aliquots. The 40  $\mu$ L aliquot was utilized for the Archimedes meter and the 200  $\mu$ L aliquot for the Siemens EXL.

**Results:** The ammonia sensor was used to produce a calibration curve. Seven measurement points produced the curve, which fall within the FDA guideline for pre-validation of a bioanalytical method. The calibration curve has an excellent  $r^2$  of 0.998. It should be noted that the calibration curve covers concentrations of blood ammonia ranging from 200-500  $\mu$ M and thus covers the entire physiologically normal to highly elevated range. The two measured values were then plotted against each other as seen in. 44 blood ammonia measurements, which include nine samples from patients with urea cycle disorders or propionic acidemia, were utilized to generate the correlational curve.

**Conclusions:** The investigated sensor can not only differentiate between healthy and emergency blood ammonia levels, but can quantify the ammonia to a reasonable enough degree for precise blood ammonia management through treatment. This would allow for a management regime similar to the one used by diabetics with a blood glucometer and insulin.

### **3. Assessment of Treatment Response by <sup>18</sup>F-Fludeoxyglucose Positron Emission Tomography (FDG-PET) in Patients with Large Vessel Vasculitis (LVV)**

Shubhasree Banerjee<sup>1</sup>, Sara Alehashemi<sup>1</sup>, Mark A. Ahlman<sup>2</sup>, Cahid Civelek<sup>2</sup>,

Elaine Novakovich<sup>3</sup>, David A. Bluemke<sup>2</sup>, Peter C. Grayson<sup>3</sup>

<sup>1</sup> Rheumatology Fellowship and Training Branch, NIAMS, NIH

<sup>2</sup> Radiology and Imaging Sciences, Clinical Center, NIH

<sup>3</sup> Vasculitis Translational Research Program, NIAMS, NIH

**Objective:** FDG-PET can be used to detect vascular inflammation in LVV. Study objective was to determine if current therapies for LVV impact vascular FDG uptake.

**Methods:** Patients with giant cell arteritis (GCA) or Takayasu's arteritis (TAK) were recruited into prospective, observational LVV cohort. Everybody underwent FDG-PET/CT at 6-month intervals. Cumulative glucocorticoid dose change between visits was calculated. Treatment status between visits was categorized as increased, decreased, or unchanged. Treatment change was defined as change in daily prednisone over past 7 days by  $\geq 5$ mg, DMARD/biologic addition/ 50% dose change. Standardized uptake values (SUVs) were measured in: 1) ascending aorta-arch; 2) descending aorta; 3) liver. Vascular FDG uptake was quantified as target to background ratio (TBR) standardized to liver. TBR change in each aortic region was calculated between visits. TBR change across treatment status categories was compared by Kruskal-Wallis test. Spearman correlation between change in TBR, change in cumulative glucocorticoid, and change in methotrexate dose was calculated. Relationship between change in methotrexate and glucocorticoid dose with TBR change was evaluated by linear regression.

**Results:** FDG-PET/CT was performed in 20 LVV patients (GCA=14;TAK=6) over 49 visits. 15 patients received glucocorticoids, 10 received methotrexate, and 8 received another DMARD/biologic. Increased, decreased and unchanged therapy were recorded over 11, 5, and 11 visit intervals respectively. There was simultaneous glucocorticoid reduction with DMARD increase over 2 intervals, which were excluded from analysis. TBR change of descending aorta significantly differed among 3 treatment categories ( $p=0.01$ ) and significant reduction in TBR in increased versus unchanged treatment groups. Similar trend was observed in ascending aorta and arch TBR among 3 treatment groups ( $p=0.08$ ). TBR change of descending aorta was inversely correlated with cumulative glucocorticoid ( $r=-0.40$ ,  $p=0.03$ ) and methotrexate dose change ( $r=-0.67$ ;  $p=0.01$ ). Changes in glucocorticoid and methotrexate dose were independently associated with descending aorta TBR change ( $p<0.05$ ).

**Conclusions:** Common therapies for LVV, glucocorticoids and methotrexate, can reduce FDG vascular uptake in aorta. Change in PET activity is more pronounced in descending aorta than ascending aorta/arch. FDG-PET might be useful to monitor vascular disease activity as an outcome measure in LVV clinical trials.

### **4. Utilization of a Craniofacial Malformation Patient Cohort to Identify Novel Syndromes Leading to Targeted Therapeutics Development**

EJ Bhoj, HH Hakonarson.

Division of Human Genetics, Center for Applied Genomics, Children's Hospital of Philadelphia

**Objective:** Current genomic technology has identified a causative gene in less than half of patients with a suspected genetic syndrome. Many undiagnosed patients harbor mutations in genes that have yet to be associated with human disease. Each unknown gene represents a new diagnosis, possible novel therapeutic target, and focus for biomedical research. We have enriched novel gene discovery by selecting patients with undiagnosed craniofacial malformation syndromes likely to have a single-gene condition. We will discover novel disease-causing genes in a cohort of highly-informative patients with syndromic craniofacial malformations and investigate the role of these genes in human disease, with a focus on potential therapeutic targets.

**Methods:** We collected 300 extensively phenotyped patients with syndromic craniofacial malformations who remain undiagnosed despite expert evaluation. These patients underwent advanced next-generation sequencing, and variants in novel genes of interest were identified by compiling information from animal models, signaling pathways, and related known disorders.

**Results:** We have identified 21 potential novel disease-causing genes in this cohort. Among these genes was *TBC1-domain-containing kinase (TBCK)*, which prompted us to establish an international collaboration focusing on 13 affected patients with intellectual disability, hypotonia, seizures, and dysmorphic facies. We demonstrated that TBCK protein is not present in lymphocytes from affected patients. As TBCK has been shown to regulate the mammalian Target of Rapamycin (mTOR) pathway, we tested levels of mTOR and S6, a downstream protein. These were unchanged, but phospho-S6, a marker of mTOR activation, was downregulated. We were able to rescue this phenotype in patient cells with leucine, an activator of mTOR, suggesting a novel therapy for this progressive disorder. In addition, multiple patients with variants in epigenetic-modifying genes have been identified, and repurposing of current therapies that target those pathways is underway.

**Conclusions:** The utility of next-generation sequencing for gene discovery can be improved by focusing on specific malformations as a marker of single-gene disorders. One syndrome found by this method was *TBCK*-related intellectual disability syndrome, which lead to repurposing of leucine as a targeted therapy.

### 5. Respiratory Manifestations in 38 Patients with Alström Syndrome

Caroline Boerwinkle<sup>1</sup>, Jan D. Marshall<sup>4, 5</sup>, Joy Bryant<sup>2</sup>, William A. Gahl, MD, PhD<sup>2</sup>,

Kenneth N. Olivier, MD, MPH<sup>1, 3</sup>, Meral Gunay-Aygun, MD<sup>2</sup>

<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

<sup>2</sup>National Human Genome Research Institute, Bethesda, MD, USA

<sup>3</sup>National Heart, Lung, and Blood Institute, Bethesda, MD, USA

<sup>4</sup>The Jackson Laboratory, Bar Harbor, ME, USA

<sup>5</sup>Alström Syndrome International, Mt Desert, ME, USA

**Objective:** Alström syndrome (AS) is a rare, autosomal recessive, primary ciliopathy characterized by retinal degeneration, sensorineural hearing loss, obesity, insulin-resistant diabetes, hypertriglyceridemia, cardiomyopathy, hepatorenal disease, and recurrent respiratory infections. Although primary and motile cilia are physiologically distinct, prior studies have suggested a phenotypic overlap between primary ciliopathies and PCD, a motile ciliopathy characterized primarily by respiratory tract disease. This study describes the burden of oto-sino-pulmonary disease in 38 individuals with AS and examines the degree of clinical overlap between PCD and AS.

**Methods:** Thirty-eight patients with mutation-confirmed AS were evaluated at the NIH Clinical Center as part of an ongoing assessment of AS. The pulmonary portion of the evaluation included chest imaging, retrospective review of the medical records, and clinical history surveys. Additionally, nine patients had nasal nitric oxide (nNO) measurements and four had nasal cilia biopsies.

**Results:** The most commonly reported oto-sino-pulmonary complications reported in AS were recurrent otitis media (92%), bronchitis/pneumonia (61%), and sinusitis (50%). Of the patients with recurrent otitis media, 54% required pressure equalization tube placement and 29% had multiple sets. Laterality defects, unexplained neonatal respiratory distress, year-round nasal congestion and wet cough were assessed as PCD-characterizing symptoms. These were far less prevalent in the AS cohort compared to the PCD population. The average nNO production in the AS cohort was  $232 \pm 57.1$  nL/min compared to a cut-off of  $< 77$  nL/min for PCD, and electron microscopy analysis of ciliary biopsies revealed no ultrastructural abnormalities.

**Conclusions:** These data suggest that the oto-sino-respiratory complications in AS are frequent and severe enough to warrant increased clinical attention, but significantly impaired respiratory cilia function as seen in PCD is unlikely in AS. (www.clinicaltrials.gov, trial NCT00068224)

Supported in part by the Intramural Research Programs of NHGRI, NIAID, and NHLBI/NIH. The Genetic Disorders of Mucociliary Clearance (U54HL096458) is part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research, NCATS, funded through a collaboration between NCATS and NHLBI.

**6. Hearing Loss and Otologic Outcomes in Fibrous Dysplasia**

Alison M Boyce<sup>1,2</sup>, Carmen Brewer<sup>3</sup>, Timothy R DeKlotz<sup>4</sup>, Christopher Zalewski<sup>3</sup>, Kelly King<sup>3</sup>, Michael T Collins<sup>1</sup>, H Jeffrey Kim<sup>3,4</sup>

<sup>1</sup>Section on Skeletal Disorders and Mineral Homeostasis, Craniofacial and Skeletal Diseases Branch,

National Institute of Dental and Craniofacial Research, NIH

<sup>2</sup>Bone Health Program, Division of Orthopaedics & Division of Endocrinology and Diabetes, Children's National Health System

<sup>3</sup>Otolaryngology Branch, National Institute on Deafness and Other Communication Disorders, NIH

<sup>4</sup>Department of Otolaryngology-Head & Neck Surgery, Georgetown University Hospital

**Objective:** Fibrous dysplasia (FD) arises from somatic activating mutations in the cAMP-regulating protein  $G_s\alpha$ , leading to replacement of normal bone by proliferative osteogenic precursors. In the craniofacial skeleton this results in formation of expansile lesions, leading to facial deformity and functional impairment. A transgenic mouse model of increased  $G_s$  signaling demonstrates severe and progressive hearing loss due to cochlear overgrowth (Akil, PLOS One 2014), however the human audologic and otologic phenotype has not been determined. The purpose of this study is to characterize audologic and otologic outcomes in patients with craniofacial FD, and to investigate mechanisms of hearing loss.

**Methods:** Clinical data from a longstanding FD natural history study at the NIH were reviewed. Subjects underwent concordant audologic and otologic evaluation, and CT imaging.

**Results:** 136 subjects with craniofacial FD were evaluated (mean age 23, range 3-80). Hearing loss was identified in 55 ears (20%), which was conductive in 12%, sensorineural in 7%, and mixed in 1%. Among those with hearing loss, the degree was characterized as mild (85%), moderate (11%), or severe (4%), and was largely non-progressive. Conductive hearing loss was highly associated with FD involving the epitympanum ( $p=0.004$ ), resulting in middle ear deformity with impingement on the ossicles ( $p=0.003$ ). These findings were verified using tympanometry, which demonstrated stiffened middle ear systems in patients with epitympanic FD ( $p<0.0001$ ). Sensorineural hearing loss was correlated with increased length of the internal auditory canal ( $p=0.02$ ), suggesting deformation of the canal with stretching of the auditory nerve is a mechanism of hearing loss.

**Conclusion:** Hearing loss is common in FD, and is typically mild and non-progressive. Conductive and sensorineural hearing loss develop from deformities affecting structures of the middle and inner ear systems, respectively. Hearing and otologic monitoring is indicated in patients with craniofacial FD.

This research was supported by the Intramural Research Program of the NIH, NIDCR.

**7. Finding the Needle in the Haystack: The Use of Whole Exome Sequencing in Determining the Pathogenic Mutations in Patients with Retinal Degeneration**

Laura Bryant, Olga Lozynska and Jean Bennett

University of Pennsylvania, Philadelphia, PA

**Objective:** Diseases causing retinal degeneration such as retinitis pigmentosa and Leber's congenital amaurosis (LCA) are caused by mutations that typically follow Mendelian genetics. Determining the pathogenic mutations in each patient can be challenging since mutations in many different genes can lead to the same disease presentation. For example, LCA has been shown to result from mutations in any of 14 different genes with 30% of the cases still from unknown mutations. Our goal is to find pathogenic mutations in patients with various forms of genetic retinal degeneration.

**Methods:** We performed whole exome sequencing on 86 patients with various form of retinal degeneration including LCA, retinitis pigmentosa, Stargardt's disease, cone rod dystrophy and achromotopsia. We then used a masked analysis to identify potentially pathogenic mutations without knowledge of the type of retinal degeneration. We then prioritized those mutations based on the diagnosis and performed segregation analysis when possible.

**Results:** We identified pathogenic mutations in 54 of the 86 patients. Most of the identified mutations are in genes that have already been linked to retinal degeneration with 21 novel mutations in genes linked to retinal degeneration. Using a masked approach to the analysis allowed us to identify several de novo mutations that caused autosomal dominant retinal degeneration when we expected an autosomal recessive mutation based on the family history as well as two cases of syndromic disease where non-syndromic retinal degeneration had been diagnosed.

**Conclusions:** Whole exome sequencing is making it easier to identify the pathogenic mutations in patients who test negative for the known mutations leading to their diagnosed form of retinal degeneration. However, we are in need of strategies to analyze the large data sets generated. We have shown that one of the most efficient initial steps is using a semi-masked analysis to pull out rare mutations in genes already known to cause any form of retinal degeneration. This can help identify novel pathogenic mutations in those genes as well as identify de novo mutations that cause dominant disease when there is no family history of retinal degeneration.

## 8. Chronic Hepatocellular Injury in Urea Cycle Disorders

Lindsay C. Burrage<sup>1</sup>, Danielle Guffey<sup>2</sup>, Charles G. Minard<sup>2</sup>, Brendan H. Lee<sup>1</sup>,  
Members of the Urea Cycle Disorders Consortium, Sandesh Nagamani<sup>1</sup>

<sup>1</sup>Department of Molecular and Human Genetics, Baylor College of Medicine

<sup>2</sup>Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine

**Objective:** Hepatocellular injury, hepatic fibrosis, and cirrhosis have been described in a subset of patients with urea cycle disorders (UCDs). Although case reports and case series suggest a higher prevalence of chronic hepatic complications in argininosuccinate lyase deficiency as compared to other disorders, the prevalence and severity of chronic hepatocellular injury or hepatic complications in various UCDs are unknown. We used data from the Longitudinal Study for Urea Cycle Disorders (n=640 subjects), a natural history study conducted by the UCDC of the Rare Diseases Clinical Research Network (RDCRN), to estimate the prevalence of chronic hepatocellular injury in various UCDs.

**Methods:** AST and ALT levels from visits were analyzed to determine the prevalence of chronic hepatocellular injury in each disorder. Regression analyses and mixed modeling were used to determine covariates associated with higher AST and ALT in patients with argininosuccinate lyase deficiency. Covariates used in the analysis included baseline age, gender, presence of hyperammonemia episodes, baseline citrulline level, baseline arginine level, baseline glutamine level, high dose arginine supplementation, use of any nitrogen-scavenging agent, use of sodium phenylbutyrate or glycerol phenylbutyrate, and use of sodium benzoate.

**Results:** The overall prevalence of chronic hepatocellular injury in this cohort was 9%. The highest prevalence of chronic hepatocellular injury was observed in argininosuccinate lyase deficiency (33%) and arginase deficiency (23%). The presence of at least one episode of hyperammonemia, use of any nitrogen-scavenging agent, use of sodium phenylbutyrate/glycerol phenylbutyrate, and use of sodium benzoate were significantly associated with higher AST and ALT in patients with argininosuccinate lyase deficiency.

**Conclusions:** These data show that chronic hepatocellular injury is a significant feature in argininosuccinate lyase deficiency and arginase deficiency. Severity of urea cycle dysfunction appears to be associated with chronic hepatocellular injury in argininosuccinate lyase deficiency. We are now leading a pilot project in the UCDC to assess liver stiffness and serum biomarkers of fibrosis in several UCDs to further pursue the clinical significance of these findings.

## 9. Preliminary Results from a Phase II study of nivolumab (anti-PD-1 antibody) for patients with metastatic adrenocortical carcinoma (ACC)

Ludimila Cavalcante<sup>1</sup> MD, Benedito Carneiro<sup>1</sup> MD, Ricardo Costa<sup>1</sup> MD, Alfred Rademaker<sup>1</sup> PhD, Francis Giles<sup>1</sup> MD  
<sup>1</sup> Northwestern University

**Introduction:** ACC has an estimated incidence of 0.7 cases per million per year. It is an exceedingly rare malignancy with no effective standard treatment options, and with many patients presenting with incurable metastatic disease at diagnosis. The 5-year survival rate is estimated at less than 15% for these metastatic patients, carrying an extremely poor prognosis. Hence, immunotherapy approaches emerge as promising treatment options, with novel checkpoint inhibitors being tested in this setting. Nivolumab, a fully human monoclonal IgG4 antibody against the programmed death-1 (PD-1) receptor on the surface of activated T-cells, acts by inhibiting the PD-1 interaction with PD-L1 and PD-L2 and unleashing an anti-tumor immune response. The drug is FDA approved in the treatment of melanoma, kidney and lung cancers, with large randomized trials showing prolonged responses and an acceptable toxicity profile.

**Objective:** To assess the efficacy of nivolumab monotherapy according to objective response rate (ORR) as assessed by RECIST 1.1 in patients with advanced adrenocortical carcinoma.

**Methods:** Patients with metastatic or locally advanced adrenocortical carcinoma with disease progression after treatment with at least one line of therapy including mitotane and/or chemotherapy and ECOG performance status of 0-3 are currently being enrolled on this phase II study and receiving treatment with nivolumab 240mg IV q2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal. Planned accrual of up to 33 patients will follow a Simon two stage design with interim analysis for efficacy after 10 evaluable patients are enrolled.

**Results:** This is a report of 7 patients evaluable for response thus far. Median age: 57 yrs; Caucasian (7/7); female (4 pts), male (3). Best overall response: progression of disease (5), pending evaluation (2); median time on study: 4 months. Reported grade 3 or 4 adverse events (AEs) possibly related to study drug: Tremor (1), Hypokalemia (1), all resolving after holding treatment. Reported Grade 1 and 2 AEs: LFT elevation (3), lower extremity edema (2), lymphopenia (1), urinary frequency (1), fatigue (1).

**Conclusions:** Nivolumab is thus far well tolerated in this population of metastatic ACC after first-line therapy. Results are pending from an interim analysis after enrollment of 10 evaluable patients to determine efficacy.

### 10. Accumulation of globotriaosylceramide (GL3) in cardiomyocytes (CM) is progressive with age and inversely correlates with baseline alpha galactosidase A (AGALA) activity in enzyme replacement therapy (ERT)-naïve Fabry patients with IVS4 + 919G>A mutation

Fu-Pang Chang<sup>a,b</sup>, Ting-Rong Hsu<sup>a</sup>, Seng-Che Hung<sup>a</sup>, Shih-Hsien Sung<sup>a</sup>, Wen-Chung Yu<sup>a</sup>, Dau-Ming Niu<sup>a</sup>, Behzad Najafian<sup>b</sup>  
<sup>a</sup>Taipei Veterans General Hospital, Taipei, Taiwan; <sup>b</sup>University of Washington, Seattle, United States

**Objective:** Cardiomyopathy is a major complication in patients with Fabry disease. Accumulation of GL3 in CM leads to disease progression. So far, there has not been a reliable method to quantify GL3 in CM at the histological level. We developed novel unbiased stereology methods to quantify average CM volume (CMV) and GL3 content in CM and correlated the results with clinical and imaging parameters.

**Methods:** Cardiac biopsies from 8 ERT-naïve male Fabry patients (age 62.5 [48–68], median [range]) with later-onset IVS4 + 919G>A mutation were studied by electron microscopy stereology. Half (4/8) of these patients had increased left ventricular mass index (LVMI).

**Results:** Patients with LVMI $\geq$ 48 g/m<sup>2</sup>, in comparison to those with LVMI<48 were older (65 $\pm$ 2 vs. 57 $\pm$ 6; p=0.045), and had 3.6 fold greater volume of GL3 inclusions per CM [V(Inc/CM)] (p=0.03) and a trend for greater CMV (71598 $\pm$ 32166 vs. 32185 $\pm$ 18914  $\mu$ m<sup>3</sup>; p=0.08). CMV increased with age (r=0.71; p=0.047). Both V(Inc/CM) (r=0.79, p=0.02) and GL3 inclusion volume density per CM [Vv(Inc/CM)] (r=0.83, p=0.01) were directly correlated with age. Moreover, V(Inc/CM) (r=-0.82, p=0.02) and Vv(Inc/CM) (r=-0.93, p=0.003) were inversely and strongly related to plasma AGALA activity. There were no significant relationships between CMV, GL3 content and plasma globotriaosylsphingosine (Lyso-GL3) level. No GL3 inclusions were found in endothelial cells, consistent with the later-onset Fabry phenotype.

**Conclusions:** GL3 accumulation in CM and CMV are progressive with age and linked to LVMI and reduced AGALA activity in Fabry patients, suggestive that early initiation of ERT may ameliorate progression of the disease. Unbiased stereology is promising in assessment of severity of Fabry cardiomyopathy and can potentially be used in assessing of its treatment efficacy.

### 11. Cellular Localization and Cl<sup>-</sup>/H<sup>+</sup> Coupling Properties of wild type CLC-5 and patient-specific mutants

Min-Hwang Chang<sup>1,3</sup>, Matthew Brown<sup>1,5</sup>, Yiran Liu<sup>2,6</sup>, Vladimir G. Gainullin<sup>2,4</sup>,  
 Peter C. Harris<sup>2,4</sup>, Michael F. Romero<sup>1,3,4</sup>, John C. Lieske<sup>1,3,4</sup>

<sup>1</sup>Physiology & Biomedical Engineering, <sup>2</sup>Biochemistry and Molecular Biology, <sup>3</sup>O'Brien Urology Research Center; <sup>4</sup>Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN <sup>5</sup>Wayne State University, Detroit, Michigan, USA, <sup>6</sup>University of Michigan, Ann Arbor, MI

**Objective** Dent disease 1, an X-linked inherited kidney disease caused by mutations in the *CLCN5* gene encoding a Cl<sup>-</sup>/H<sup>+</sup> exchanger (CLC-5), is characterized by low molecular weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis, nephrolithiasis, rickets, and progressive renal failure. Through systematic study of CLC-5 mutational effects on Cl<sup>-</sup>/H<sup>+</sup> exchanger activity, we try to understand the mechanisms of CLC-5 dysfunction that cause disease.

**Methods** We study common and novel mutations identified in Dent patients through Rare Kidney Stone Consortium. WT and mutant CLC-5 were expressed in *Xenopus* oocytes and Cl<sup>-</sup>/H<sup>+</sup> exchanger activity were studied using ion selective microelectrodes. Cellular localization and protein trafficking of WT and mutant CLC-5 in renal epithelial cells were also examined by immunofluorescence microscopy using eGFP/HA double-tagged CLC-5 and organelle-specific markers and quantified by flow cytometry.

**Results** The stoichiometry of WT CLC-5 was calculated to be 1.80  $\pm$  0.02 (nCl<sup>-</sup>:H<sup>+</sup>) in ND96, similar to the stoichiometry estimated for T657S. However, the stoichiometry was significantly altered for S244L, R345W, and Q629X. WT CLC-5 acts as Cl<sup>-</sup>/H<sup>+</sup> exchanger at +40mV with 104 mM Cl<sup>-</sup> in the extracellular solution. Lowering extracellular Cl<sup>-</sup> reverses the transport direction, but functions at a significantly slower rate. Although S244L has normal surface expression, S244L and R345W mutations have significantly decreased pH and Cl<sup>-</sup> exchange rates in response to solution manipulations, suggesting these mutations have an altered ion exchange coupling ratio (stoichiometry). Interestingly, while R345W was retained in the ER suggesting defective protein maturation, R345W surface localization was rescued by lowering the incubation temperature from 37 to 30°C. Q629X was retained in the ER, not localized in early endosomes, and also has abolished Cl<sup>-</sup>/H<sup>+</sup> exchange activity, suggesting that Q629X affects protein maturation and trafficking while T657S is a benign, non-disease causing mutation.

**Conclusions** These data suggest studying CLC-5 mutational effects on both transport function and cellular localization is essential to better understand divergent phenotypes in Dent disease.

**Funding:** R25DK101405, U54DK083908, U54DK100227



## 12. Acute Intermittent Porphyria: Low Penetrance of the Autosomal Dominant Disease Indicates a Significant Role of Genetic Modifiers in Disease Pathogenesis

Brenden Chen, Constanza Solis-Villa, Jörg Hakenberg, Wanqiong Qiao, Ramakrishnan R. Srinivasan, Makiko Yasuda, Manisha Balwani, Dana Doheny, Inga Peter, Rong Chen, Robert J. Desnick  
Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

**Background & Objective:** Acute Intermittent Porphyria (AIP), the most common hepatic porphyria, results from hydroxymethylbilane synthase (*HMBS*) mutations that markedly decrease *HMBS* enzymatic activity. Typically, this autosomal dominant disease is diagnosed when heterozygotes have life-threatening acute neurovisceral attacks, while most heterozygotes remain asymptomatic and undiagnosed. Although >400 rare *HMBS* mutations have been reported, the prevalence of pathogenic *HMBS* mutations in genomic/exomic databases, and the actual disease penetrance have not been investigated.

**Methods:** To estimate the prevalence of pathogenic *HMBS* mutations in various demographic/racial groups, we interrogated genomic/exomic databases, identified non-synonymous and consensus splice-site variants, and determined the pathogenicity of the non-synonymous variants by *in vitro* expression assays and *in silico* prediction programs. To identify potential genetic modifiers, 8 AIP patients with recurrent attacks and their asymptomatic parents and siblings (total: 27 individuals) were recruited and sequenced for 108 heme biosynthesis related genes using customized capture array.

**Results:** Caucasians had the most variants, 58 non-synonymous and two consensus splice-site variants among ~92,000 alleles with a combined allele frequency of 0.00575 (1/174). *In silico* programs predicted 14/58 (24%) non-synonymous variants as “likely-pathogenic”. *In vitro* expression identified seven variants with  $\leq 3\%$  of wild-type (WT) activity and three with residual activities that were markedly thermolabile. The combined allele frequency of these 10 “likely-pathogenic” non-synonymous and two consensus splice-site variants was 0.00056 (1/1,782). Notably, six presumably pathogenic non-synonymous variants listed in the Human Gene Mutation Database were benign. Compared to the recent prevalence estimate of symptomatic heterozygotes in Europe (~0.000005), the prevalence of likely-pathogenic *HMBS* mutations among Caucasians was >100 times more frequent. The 108-gene capture array identified 8 novel and 16 rare SNPs (allele frequency <0.01) as likely protective alleles and 3 novel and 4 rare SNPs (allele frequency <0.045) as likely susceptibility alleles that are statistically significantly associated with the 8 AIP patients.

**Conclusions:** These findings indicate the penetrance of acute attacks was ~1% of heterozygotes with likely-pathogenic mutations. Current efforts are to validate the genetic association and to elucidate the functional impacts of the 31 alleles with AIP pathogenesis.

## 13. Impact of dietary intake on bone turnover in patients with phenylalanine hydroxylase deficiency

Kathryn E Coakley<sup>1</sup>, Eric I Felner<sup>2</sup>, Vin Tangpricha<sup>3</sup>, Peter W Wilson<sup>4</sup>, Rani H Singh<sup>5</sup>

<sup>1</sup>Nutrition and Health Science Program, Laney Graduate School, Emory University, Atlanta, GA, <sup>2</sup>Associate Professor of Pediatrics, Division of Pediatric Endocrinology, Emory University School of Medicine, Atlanta, GA, <sup>3</sup>Associate Professor, Division of Endocrinology, Metabolism and Lipids, Emory University School of Medicine, Atlanta VA Medical Center, Atlanta, GA,

<sup>4</sup>Clinical Cardiovascular Research Institute, School of Medicine, Emory University, Atlanta, GA, <sup>5</sup>Metabolic Nutrition Program, Department of Human Genetics, School of Medicine, Emory University, Atlanta, GA

**Objective:** Phenylalanine hydroxylase (PAH) deficiency is a genetic disorder characterized by deficiency of the PAH enzyme. Patients cannot metabolize the amino acid, phenylalanine, and follow a phenylalanine-restricted diet low in intact protein. Patients are prescribed synthetic medical food (MF) supplying a phenylalanine-free protein source. This study assessed the impact of dietary intake and nutrient source (food versus MF) on bone mineral density (BMD) and bone turnover markers (BTM) in patients with PAH deficiency. Differences in variables were examined by age groups and correlations between bone indicators were assessed.

**Methods:** Blood from 44 fasted females ages 11-52 years was analyzed for plasma phenylalanine and serum BTM [CTx (resorption), P1NP (formation)], vitamin D, and parathyroid hormone (PTH). A BTM ratio was calculated to assess resorption relative to formation (CTx/P1NP). Dual energy x-ray absorptiometry measured body composition, BMD, and BMD Z-scores. Three-day food records were analyzed for total nutrient intake, nutrients by source (food versus MF) and compliance with MF prescription. Spearman's partial correlations adjusting for age, BMI, energy intake and blood phenylalanine were calculated to assess correlations.

**Results:** All subjects had normal BMD (Z-score>-2). Sixty-four percent had high CTx (resorption) and normal P1NP (formation) indicating uncoupled bone turnover. CTx/P1NP was positively associated with food phenylalanine ( $r^2=0.39$ ;p-value=0.017), energy ( $r^2=0.41$ ;p-value=0.011) and zinc ( $r^2=0.41$ ;p-value=0.014). CTx/P1NP was negatively associated with MF fat ( $r^2=-0.44$ ;p-value=0.008), MF compliance ( $r^2=-0.34$ ;p-value=0.056), and positively with food sodium ( $r^2=0.43$ ;p-value=0.014). CTx/P1NP decreased significantly with age (p-value=0.002) and higher PTH (p-value=0.0002). Other indicators were not correlated, including plasma phenylalanine with any bone indicators.

**Conclusions:** Females with PAH deficiency had normal BMD but elevated BTM, indicating high bone resorption. Younger patients had a less favorable BTM ratio; more favorable ratios were associated with nutrients from MF and compliance. Promoting adequate micronutrient intake through optimal compliance with MF likely impacts bone more than phenylalanine in patients with PAH deficiency.

#### 14. $\beta$ -Cyclodextrin Polyrotaxanes as Potential Niemann-Pick Type C Therapeutics:

##### From Design to In Vivo Therapeutic Efficacy

C. J. Collins<sup>1</sup>, Y. Mondjinou<sup>1</sup>, S. Alam<sup>2</sup>, B. Loren<sup>1</sup>, K. Halder<sup>2</sup>, D. H. Thompson<sup>1</sup>

<sup>1</sup>Purdue University, West Lafayette, IN 47906. <sup>2</sup>University of Notre Dame, Notre Dame, IN 46556.

**Objective:** Niemann-Pick Type C disease (NPC) is a rare metabolic disorder characterized by aberrant accumulation of cholesterol within the late endosome/lysosome. Ranges of visceral and neurological symptoms present clinically- including a progressive neurodegeneration. NPC is ultimately fatal and there are no FDA approved treatments currently available to patients. 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD), a small molecule glucose macrocycle, has been shown to be an effective NPC therapeutic, with administration increasing the average lifetime of NPC mice by as much as 50% and delaying neurodegeneration. Although promising, HP- $\beta$ -CD has poor bioavailability due to rapid renal filtration. We sought to design high molecular weight, HP- $\beta$ -CD pro-drug delivery vehicles, known as polyrotaxanes (PR) to prevent rapid excretion and improve the bioavailability of each dose.

**Methods:** A family of PR materials has been generated using a variety of  $\beta$  CD derivatives and triblock co-polymers for comparison of their pharmacokinetic profiles, toxicities, and therapeutic efficacy.

**Results:** In vitro, PR localize to the late endosome/lysosome of NPC cells and mobilize cholesterol from sites of abnormal sequestration. [1] In vivo, PR are affected by the structure and dynamics of their rod-like morphologies. We show that highly threaded PR circulate for up to 24 hours and deposit in the liver, whereas lung deposition and rapid clearance is observed for PR with lower threading percentages. In contrast, physiochemical differences have little influence on toxicity. [2] PR administration effectively diminishes sequestered cholesterol within the visceral organs of NPC mice at molar concentrations 10-to-100-fold lower than HP- $\beta$ -CD. PR architectures featuring increased threading and high polymer core hydrophobicity appear to generate enhanced therapeutic efficacy.

**Conclusions:** Presented herein is the full course of PR development as potential NPC treatment- from design to therapeutic efficacy in vivo. In all, PR scaffolds hold great promise for clinical translation as potential treatments for NPC patients.

1. C. J. Collins, et Al., "Synthesis, Characterization, and Evaluation of Pluronic-based  $\beta$ -Cyclodextrin Polyrotaxanes for Mobilization of Accumulated Cholesterol from Niemann-Pick Type C Fibroblasts" *Biochemistry* 2013 52, 3242-3253.

2. C. J. Collins, et. Al. "Influence of Molecular Structure on the In Vivo Performance of Flexible Rod Polyrotaxanes", *Biomacromolecules*, DOI: 10.1021/acs.biomac.6b00508.

#### 15. Idiopathic Bronchiectasis and Heritable Connective Tissue Disorders: A Reflection of Shared Genetic Variation

M. Leigh Anne Daniels MD, MPH; Maimoona A Zariwala PhD; Michael R. Knowles MD

University of North Carolina, Chapel Hill, NC

**Objective:** Idiopathic bronchiectasis (IB) patients demonstrate phenotypic features, such as an asthenic body morphotype, pectus deformity, scoliosis, and hypermobility; plus an association with pulmonary NTM infection. These features, plus dural ectasia, also occur in individuals with heritable connective tissue disorders (HCTD). Our prior data showed that lumbar dural sac size in IB patients is enlarged as compared to healthy ( $p < 0.001$ ) and bronchiectasis controls ( $p = 0.002$ ). Our objective is to test whether IB patients have enlargement (ectasia) of the dural sac of the thoracolumbar spine as determined by chest CT; if true, this would support our hypothesis that variants in genes associated with HCTD pathogenesis underlie the development of idiopathic bronchiectasis.

**Methods:** Using a validated assessment method that is not affected by age, gender, or height (Daniels, *Clin Radiol* 2015), dural sac size in IB patients was measured by two readers, blinded to diagnosis, using MR images of the lumbar spine and CT images of the thoracolumbar spine. Dural sac measures at the mid corpus level of L1-L5 (MRI) and T10-L1 (CT) were compared in individuals with both types of imaging (63 IB, 49 control, and 22 Marfan).

**Results:** In IB, lumbar dural sac size is enlarged as compared to healthy ( $p < 0.001$ ) and bronchiectasis controls ( $p = 0.002$ ). Lumbar dural sac size is associated with pulmonary nontuberculous mycobacterial infection ( $p = 0.007$ ), long fingers ( $p = 0.003$ ), scoliosis ( $p = 0.130$ ), and family history of bronchiectasis ( $p = 0.149$ ) (Daniels, *AnnalsATS* 2016). Dural sac size can be accurately quantitated using chest CT with good correlation to MR ( $r = 0.73$ ). On CT imaging, IB subjects have significantly larger T12-L1 (average) AP-DSD as compared to controls (combined healthy and disease controls) ( $p < 0.001$ ).

**Conclusions:** These findings are consistent with IB patients having dural sac enlargement, and supports our hypothesis that IB patients have underlying genetic variation in heritable connective tissue genes. As part of the GDMCC IB research study protocol, all patients have chest CT images available in the database for quantitative assessment, allowing further phenotypic characterization of a large national cohort. Use of this novel biomarker in a large IB cohort facilitates interpretation of whole exome sequencing, and candidate gene testing in a well-phenotyped IB cohort. Current genetic analysis is focused on IB individuals with a family history of bronchiectasis.

# **16. Correlation of chest CT findings to spirometry in children with primary ciliary dyskinesia**

Ashley Deschamp<sup>1</sup>, Matthew Cooper<sup>2</sup>, Brandon Brown<sup>2</sup>, Mark Baskin<sup>2</sup>, Sarah Kleiman<sup>1</sup>, Thomas Ferkol<sup>3</sup>, Margaret Rosenfeld<sup>4</sup>, Hye-Seung Lee<sup>5</sup>, Sharon Dell<sup>6</sup>, Scott Sagel<sup>7</sup>, Carlos Milla<sup>8</sup>, Michael Knowles<sup>9</sup>, Margaret Leigh<sup>10</sup>, Stephanie Davis<sup>1</sup>.

<sup>1</sup>Department of Pediatrics and <sup>2</sup>Radiology, Indiana University School of Medicine; <sup>3</sup>Department of Pediatrics, Washington University School of Medicine; <sup>4</sup>Department of Pediatrics, University of Washington; <sup>5</sup>

Department of Pediatrics, University of South Florida; <sup>6</sup>Department of Pediatrics, University of Toronto;

<sup>7</sup>Department of Pediatrics, University of Colorado School of Medicine; <sup>8</sup>Department of Pediatrics, Stanford University;

<sup>9</sup>Department of Medicine and <sup>10</sup>Pediatrics, University of North Carolina School of Medicine.

**Objective** To evaluate chest computed tomography (CT) findings in children with PCD using a semi-quantitative scoring system and correlate with spirometry.

**Methods** Participants <19 years old with a confirmed diagnosis of PCD were recruited at sites in the Genetic Disorders of Mucociliary Clearance Consortium and evaluated prospectively with chest CT and spirometry. Chest CTs were scored using a previously published, semi-quantitative scoring method with the lung divided into 6 lobes. Each lobe was evaluated for peribronchial thickening, bronchiectasis, hyperinflation, parenchymal abnormalities, and mucus plugging and assigned a number score.

**Results** Chest CTs were scored in 77 participants, 39 males (51%) with mean age 8.4 years (SD 4.3). 87% of participants had bronchiectasis, average 3.2 affected lobes (SD 2.1). In 63%, the bronchus measured >1 but <2x the diameter of the accompanying vessel. Consolidation was present in 83% of subjects, average 1.8 affected lobes (SD 1.3). Mucus plugging was present in 45% of subjects, average 0.9 affected lobes (SD 1.3); the majority (92%) showed a tree in bud pattern. Age positively correlated with chest CT findings, especially bronchiectasis extent and severity ( $r=0.51$  and  $r=0.63$  respectively,  $p<0.0001$ ). Spirometry within 3 months of chest CT was performed in 58 participants. The size of mucus plugs on CT ("tree and bud indicating small plugs" and "large plugs") most strongly correlated with spirometric measures including FVC, FEV1 and FEF25-75 ( $r=-0.35$   $p=0.009$ ,  $r=-0.39$   $p=0.003$ ,  $r=-0.33$   $p=0.01$ , respectively).

**Conclusions** Using semi-quantitative chest CT scoring, we demonstrate lung pathology in children with PCD, the majority already with bronchiectasis. The correlations between chest CT scores and spirometry were modest, most notably between FEV1 and mucus plugging. Children with PCD have significant structural lung disease and airflow limitation.

**Funding:** NIH U54 HL09640958-09 and R01HL071798 (funded by Office of Rare Diseases Research and administered by NHLBI).

# **17. Defining Hand Stereotypies in Rett Syndrome: A Movement Disorders Perspective**

Marisela E. Dy<sup>1,2</sup>, Jeff L. Waugh<sup>1,2</sup>, Nutan Sharma<sup>1,2</sup>, Heather O'Leary<sup>1</sup>, Kush Kapur<sup>1</sup>, Alissa D' Gama<sup>3</sup>, Mustafa Sahin<sup>1</sup>, David K. Urion<sup>1</sup>, Walter E. Kaufmann<sup>1</sup>

<sup>1</sup>Boston Children's Hospital, <sup>2</sup>Massachusetts General Hospital, <sup>3</sup>Harvard Medical School

**Objective:** Hand stereotypies (HS) are a primary diagnostic criterion for Rett Syndrome. Few publications have quantified HS and none have used a completely blind rating. We endeavored to develop a protocol for systematic characterization and quantification of HS in Rett Syndrome.

**Methods:** Videotaped recordings with simultaneous actigraphy were collected on 24 subjects who participated in a phase 2 clinical trial with IGF-1 (NCT01777542), prior to their first subcutaneous injection of drug/placebo. Two 5-minute periods were reviewed for each subject to identify the 2 most common HS. Three independent raters (movement disorders neurologists) reviewed the 5-minute windows using established terminology to determine level of agreement. The protocol was revised in 3 iterative stages to improve descriptive accuracy; 10 of the videos (chosen randomly) were re-reviewed by the same 3 raters using the new protocol. Agreement among raters was analyzed using Kappa statistics.

**Results:** The initial protocol was applied to 24 subjects; when the hands were rated together, there was a 20.7 percent agreement among the 3 raters. The protocol was refined further, including "central" and "peripheral" categories that were further stratified as "simple" or "complex". "Mouthing" was included under "central" category. Each hand was scored separately. A higher level of agreement was found using the new protocol for each hand (right/left) and the two most frequent HS (HS1, HS2): HS1 left 50.8%, HS1 right 42.2%, HS2 left 21.2%, HS2 right 29.5%.

**Conclusions:** Phenotypic variability in HS makes standardized evaluation a challenge; we achieved only 50% level of agreement, but only for the most frequent HS. Therefore, objective measures (such as actigraphy) are needed to evaluate HS.

*This work was supported by a Mentored Training Fellowship through Rettsyndrome.org under the U54 HD061222 NIH grant.*

**18. Implications of Glycolate Metabolism on Mitochondria in Primary Hyperoxaluria**

Sonia Fargue<sup>1</sup>, Tanecia Mitchell<sup>1</sup>, John Knight<sup>1</sup>, Ross P. Holmes<sup>1</sup>

<sup>1</sup> University of Alabama at Birmingham. Department of Urology, Birmingham, AL.

**Objective:** The primary hyperoxalurias (PH) are a group of severe inherited disorders in the metabolism of glyoxylate. They are characterized by an increased endogenous production of oxalate and calcium oxalate kidney stones in patients that can lead to end-stage renal failure. Glyoxylate is a precursor of oxalate and is the substrate of alanine:glyoxylate aminotransferase (AGT, deficient in PH1) or glyoxylate reductase (GR, deficient in PH2). In PH1, excessive amounts of glycolate are presumed to be the result of glyoxylate to glycolate cycling in the presence of GR and another enzyme, glycolate oxidase (GO). Both oxalate and glyoxylate have been linked with oxidative stress. The objective of this study was to test the hypothesis that lack of functional AGT and GR, as is the case in PH, results in mitochondrial dysfunction through changes in the synthesis of glycolate and glyoxylate

**Methods:** Previously established transformed CHO cells expressing GO  $\pm$  AGT or GR were incubated with various concentrations of glycolate, glyoxylate or oxalate (0-200  $\mu$ M) for up to 24h. The intra and extracellular concentrations of oxalate, glycolate and glyoxylate was measured by IC/MS and HPLC. The mitochondrial function was measured with a Seahorse XF-96 extracellular flux analyzer.

**Results:** Glycolate to glyoxylate cycling was shown to occur in the presence of both GO and GR. The metabolism of glycolate by GO generated glyoxylate and oxalate concomitantly with intracellular ROS and decreased cell viability. At concentrations as low as 50  $\mu$ M, glycolate metabolism was responsible for a greater than 50% decrease in mitochondrial maximal respiration and reserve capacity after 4h. Glyoxylate, but not oxalate decreased mitochondrial respiration. The co-expression of either AGT or GR reduced oxalate and glyoxylate synthesis, although intracellular levels remained high with expression of GR. Both AGT, and to a lesser extent GR, decreased but did not prevent the mitochondrial dysfunction.

**Conclusion:** The disruption of normal glycolate/glyoxylate metabolism, seen in deficiencies of AGT or GR, is responsible for mitochondrial dysfunction. Both liver and kidney are involved in glyoxylate metabolism. The long-term consequences of mitochondrial stress in those organs in Primary Hyperoxaluria warrant investigations as novel therapies aimed at protecting mitochondria become available.

**19. Phenotypic Characteristics of Phelan-McDermid Syndrome from the Phelan-McDermid Syndrome International Registry**

Cristan Farmer<sup>1</sup>, Audrey Thurm<sup>1</sup>, Jill Leon<sup>1</sup>, Latha Soorya<sup>2</sup>, Megan O'Boyle<sup>3</sup>, Rebecca Davis<sup>3</sup>, & Paul Avillach<sup>4</sup>

<sup>1</sup>National Institute of Mental Health, <sup>2</sup>Rush University Medical Center, <sup>3</sup>Phelan-McDermid Syndrome Foundation, <sup>4</sup>Harvard Medical School

**Objective:** Phelan-McDermid Syndrome (PMS) is a neurogenic condition that affects individuals based on deletions or mutation in the distal end of the long arm of chromosome 22. The few systematic studies of the cognitive and behavioral phenotype of PMS that have been conducted indicate that intellectual disability and limited verbal ability is common, along with delayed developmental milestones in across all domains. Medical features, including epilepsy and gastrointestinal problems, are also commonly reported. Data from a large number of individuals with PMS are now available through the PMS Foundation's online international registry. The current study uses this registry to obtain estimated prevalence rates for cognitive, language, and medical impairments.

**Method:** Access was requested and granted for aggregate data available in the PMS International Registry (see: <https://pmsiregistry.patientcrossroads.org/>), which includes data from 981 individuals (July 1, 2016). The current study uses data from clinical questionnaires, including a developmental questionnaire (N=441; mean age=12.72 years, range=8-20 years). Caregiver answers were used to describe behavioral and medical phenotypic characteristics. A subset of participants have agreed to participate in the PMS Data Network, which includes the collection of electronic health records and clinical notes.

**Results:** In response to a question about their child's communicative ability (for children aged 2+ years), 23% of 441 individuals indicated that their child communicates verbally, and 9% were reported to understand complex commands. Independent toileting was reported to be achieved consistently in 13%. Parents reported that 84% of 403 individuals walked independently, with 30% of the sample reported to achieve independent walking by 18 months. Responses to questions regarding seizures indicated that 29% have experienced non-febrile seizures (including absence, complex partial, simple partial, tonic-clonic and "other"). Details of response data to these and other questions will be provided.

**Conclusions:** Until results become available from systematic, clinic-based natural history studies of PMS, results from registry data such as these represent our current understanding of the PMS phenotype. These results confirm description in the literature of pervasive motor, communication, and daily living skill impairments, and create the beginning profile for the development of severity measures to be used in treatment trials that are underway for this syndrome.

## 20. Clinical Presentations of Relapsing Polychondritis: More Than a Swollen Ear

<sup>1,2,3</sup>Marcela A. Ferrada, M.D., <sup>2</sup>Ninet Sinaii PhD, MPH <sup>3</sup>Shubhasree Choudhury MD, Thomas Christie<sup>4</sup> and <sup>3</sup>James D. Katz, M.D.  
<sup>1</sup>Critical Care Department National Institutes of Health, Bethesda, MD, <sup>2</sup>National Institutes of Health Clinical Center, Bethesda, MD,  
<sup>3</sup>National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD  
<sup>4</sup>Relapsing Polychondritis Awareness and Support Foundation

**Objective:** Relapsing polychondritis (RP) is a rare and in some cases fatal autoimmune disease. Patients may have involvement of organs other than the nasal bridge and ear. Here we report the results of the largest survey to date evaluating disease patterns in an international cohort.

**Methods:** Data were acquired using an internet-based questionnaire. We obtained an Office of Human Subjects Research Protections 'Exclusion from IRB Review' certificate according to the requirements of 45 CFR 46 and NIH policy. The Relapsing Polychondritis Awareness and Support Foundation administered the survey by email solicitation to patients that previously agreed to be contacted and by posting the link online. The survey was open on 2/23/2016 and closed 8/8/2016.

**Results:** 320 surveys were captured and 16 were excluded either for age less than 18 or no age reported; thus, 304 surveys were included in this analysis. The mean age was 48.6 (SD 11.2). 87% were female. 29% reported country of origin other than the USA. The approximate mean age at diagnosis was 43.2 years (SD 12.2). A non-rheumatologist physician made the diagnosis in 44%. 56% of the patients saw more than 3 physicians prior to establishing a diagnosis. 64% of the patients had symptoms for more than 5 years before diagnosis. 54% of patients went to the emergency room prior to diagnosis because of RP symptoms.

Common (>35%) reported initial symptoms included eye inflammation, costochondritis, shortness of breath, nose pain, ear pain, knee pain, and voice changes. Complications of RP include disability (21%) and tracheomalacia (16%).

**Conclusions:** This is the largest RP study to describe patient and disease characteristics in an international, self-reported cohort. We found that there was a high prevalence of initial symptoms other than ear and nose inflammation. The time to diagnosis was usually several years. Non-rheumatologist physicians commonly encounter patients with RP, and about half of the time, these encounters occur in the emergency room. Complications due to RP include tracheomalacia and disability. Physicians must be alert to underappreciated presenting symptoms such as voice changes and shortness of breath.

## 21. Characterizing Sleep in Rett Syndrome Using Actigraphy

Alyssa M. Merbler<sup>1</sup>, Breanne J. Byiers<sup>1</sup>, John J. Garcia<sup>2</sup>, Timothy J. Feyma<sup>2</sup>, & Frank J. Symons<sup>1</sup>  
<sup>1</sup>Department of Educational Psychology, University of Minnesota, Minneapolis, MN  
<sup>2</sup>Gillette Children's Specialty Healthcare, St. Paul, MN

**Objective:** To better understand sleep regulation in Rett Syndrome Patients.

**Methods:** The present study aimed to replicate and expand upon previous work by measuring sleep with an actigraph device in a sample of girls with clinically diagnosed RTT (N = 13, mean age = 9 years, 1-17).

**Results:** The means for this sample as measured by actigraphy were: 492.3 (SD = 47.3) mins of TNS, 76.0% (SD = 6.7) sleep efficiency, and 86.0 mins (SD = 34.2) of wake after sleep onset. All participants napped at least once. No age-related changes were observed for any sleep characteristic. Parents reported a mean of 97.0 more minutes (SD = 105.2) of TNS than measured by actigraphy. Parent report and actigraphy measured TNS were moderately correlated (ICC = 0.57, p < .001, df = 77), although correlation values differed substantially across participants.

**Conclusions:** Overall, the results replicated some aspects of previous studies (e.g., no age-related changes in total nighttime sleep or efficiency). Some participants had TNS that fell into the National Sleep Foundation's recommended range, but all but one participant had low sleep efficiency. Future work could be prospectively designed and include a typically developing comparison sample to improve the precision of our understanding of sleep in RTT.



## 22. Gluteus Maximus Activation during Ambulation in Children with Osteogenesis Imperfecta (OI)

<sup>1</sup>Jessica Fritz, <sup>2</sup>Peter Smith & <sup>1,2</sup>Gerald Harris

<sup>1</sup>Marquette University/Medical College of Wisconsin, Milwaukee, WI;

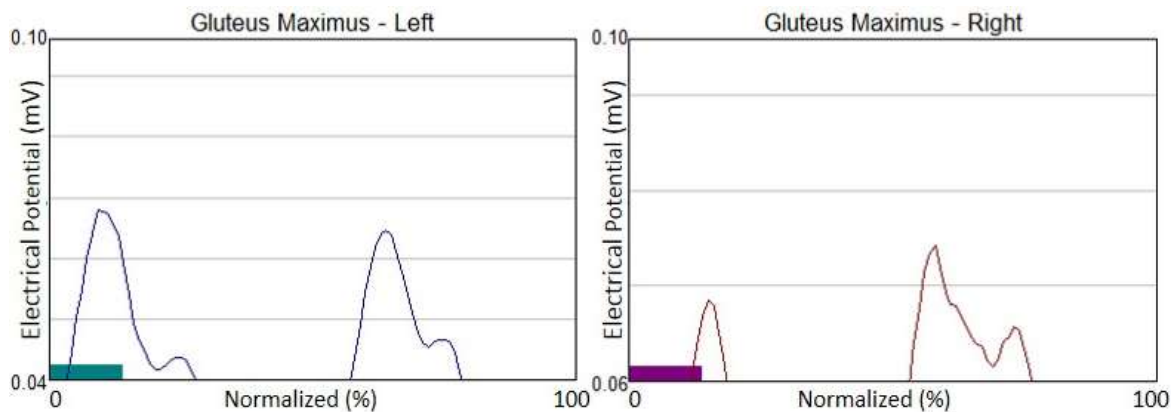
<sup>2</sup>Shriners Hospitals for Children, Chicago, IL

**Objective** This study's goal was to determine alterations in gluteus maximus activation timing during ambulation in children with OI.

**Methods** Ten children with OI type I (six females, four males;  $9 \pm 4.99$  years) and ten typically developing age- and gender-matched children (six females, four males;  $10 \pm 4.50$  years) were enrolled. Participants signed informed consent/assent to participate in the IRB-approved study. All participants underwent gait analysis, including surface electromyography (EMG) of the gluteus maximus (GM). EMG data were processed through linear envelope filtering with a 6 Hz cutoff frequency. The electrical potential was plotted versus normalized gait cycle (%). Activity of the GM was assessed through threshold ( $y_t$ ) calculation:  $y_t = \mu + \sigma \times 3$ .

Here,  $\mu$  and  $\sigma$  are the mean and standard deviation of the electrical potential during inactivity. The muscle was determined to be "on" when its value was equal to or exceeded  $y_t$  and "off" otherwise. Activation timing and spatial-temporal gait parameters were assessed.

**Results** Welch's t-tests showed that the OI population exhibited significantly prolonged double limb support, a slower walking speed and delayed GM activation during the loading response phase of gait compared to controls (Figure 1).



**Figure 1** Representative gluteus maximus (GM) average linear envelope EMG plots from a single subject with OI type I. The shaded bars along the x-axis represent normal muscle activation timing. The y-axis origin of each plot is set to the muscle's  $y_t$  value.

**Conclusions** This is the first study to examine GM activation timing during gait in OI. The altered gait parameters are consistent with previous studies. The delayed gluteus maximus activation may be due to decreased walking speed and a compensatory mechanism to reduce femur loading. The results of this study and previous work demonstrating the impact of gluteal forces on femoral stress/strain indicate a need for further study of lower body muscle timing and force production during gait in OI.

### 23. Gait Deviations in Children with Osteogenesis Imperfecta

Christina Garman<sup>1</sup>, Adam Graf<sup>2</sup>, Joseph Krzak<sup>2</sup>, Angela Caudill<sup>2</sup>, Peter Smith<sup>2</sup>, and Gerald Harris<sup>1,2</sup>

<sup>1</sup>Marquette University, Milwaukee WI,

<sup>2</sup>Shriners Hospitals for Children Chicago, Chicago IL

**Objective:** The purpose of this study was to quantitatively compare gait abnormalities in children with OI type I (mild), type III (severe) and type IV (moderate) and to determine how these abnormalities are affected by OI severity.

**Methods:** Forty-four subjects with type I ( $11.7 \pm 3.08$  yo), 12 subjects with type IV ( $10.4 \pm 2.94$  yo), 6 subjects with type III ( $12.5 \pm 3.8$  yo), and 30 controls ( $9.54 \pm 3.1$  yo) gave their informed consent to participate in the study. 3D gait analysis was performed with a 14-camera motion analysis system (MX model, Vicon Motion Systems Inc., L.A, CA) and gait parameters were calculated using the Plug-In Gait Model. To evaluate group differences, spatial temporal, kinematic and kinetic variables were compared using a multivariate analysis of variance (MANOVA) with significance concluded at a Bonferonni corrected value of  $p < 0.001$ .

**Results:** Table 1 shows results for the gait deviation index (GDI: lower GDI corresponds to greater gait pathology) and spatial, temporal, kinematic and kinetic data. Note: \* OI group is significantly different then control,  $\delta$  OI type I or OI type IV is significantly different then OI type III and  $\beta$  OI type I is significantly different then type IV

Variable	TD		Type I		p	Type IV		p	Type III		p
	Mean	SE	Mean	SE		Mean	SE		Mean	SE	
GDI	91.52	2.03	78.78	1.64	* $\delta\beta$	64.11	3.17	*	51.59	4.48	*
<b>Spatial Temporal</b>											
Walking Speed (m/s)	1.17	0.03	0.98	0.03	* $\delta$	0.93	0.05	* $\delta$	0.52	0.08	*
Cadence (Steps/min)	60.37	1.32	59.25	1.07	$\delta$	62.49	2.06	$\delta$	52.08	2.91	*
Single Support %	0.40	0.01	0.38	0.00	* $\delta$	0.37	0.01	* $\delta$	0.31	0.01	*
Double Support %	0.21	0.01	0.25	0.01	* $\delta$	0.27	0.02	* $\delta$	0.38	0.03	*
Stride Length (m)	1.17	0.03	1.00	0.02	* $\delta\beta$	0.87	0.04	* $\delta$	0.59	0.06	*
Step Length (m)	0.61	0.01	0.54	0.01	* $\delta\beta$	0.48	0.02	* $\delta$	0.35	0.03	*
<b>Kinematic</b>											
Pelvic Tilt Min (degrees)	10.50	2.71	13.62	1.18	$\delta$	16.96	2.27		20.58	3.20	*
Pelvic Tilt Max (degrees)	15.07	2.71	18.69	1.28	$\delta$	23.23	2.47	*	30.85	3.47	*
Pelvic Obliquity Min (degrees)	-4.43	0.68	-4.56	0.27	$\beta$	-5.79	0.53		-5.46	0.80	
Pelvic Obliquity Max (degrees)	4.10	0.38	4.61	0.27	$\beta$	6.16	0.53	*	5.79	0.79	
Pelvic Rotation Min (degrees)	-5.37	1.19	-6.52	0.47	$\delta$	-8.09	0.95		-10.25	1.41	*
Pelvic Rotation Max (degrees)	5.75	1.21	7.55	0.49	$\delta$	9.49	0.98	*	11.59	1.44	*
Hip Flexion Min (degrees)	-6.34	2.03	-2.54	1.63	$\delta\beta$	6.76	3.15	*	12.23	4.44	*
Hip Flexion Max (degrees)	37.47	1.86	41.25	1.50	$\delta\beta$	48.35	2.89	*	50.57	4.08	*
Hip Adduction Min (degrees)	-8.30	1.83	-8.18	0.82	$\delta$	-11.07	1.60	*	-16.27	2.29	*
Hip Adduction Max (degrees)	4.87	2.20	4.72	1.00		2.48	1.95		-0.60	2.77	*
Hip Rotation Min (degrees)	-1.04	3.83	-9.73	1.67	* $\delta\beta$	-22.96	3.30	*	-21.31	4.60	*
Hip Rotation Max (degrees)	15.16	3.48	5.28	1.60	* $\beta$	-7.94	3.11	*	-1.17	4.23	*
Knee Flexion Min (degrees)	1.26	1.43	-0.34	1.14	$\beta$	7.65	2.20	*	5.66	3.11	
Ankle Peak Dorsiflexion (degrees)	16.49	1.36	15.58	0.98	$\delta$	16.68	1.94	$\delta$	23.75	2.84	*
Ankle Peak Range (degrees)	32.77	0.97	28.73	0.76	*	29.17	1.48	*	32.14	2.10	
Foot Progression Min (degrees)	-18.37	2.10	-22.93	1.67		-26.25	3.23	*	-22.68	4.57	
Foot Progression Max (degrees)	-3.18	1.85	-7.14	1.46	$\delta$	-7.49	2.83		1.62	4.01	
<b>Kinetics</b>											
Hip Peak Flexion (Nm/kg)	0.90	0.05	0.56	0.04	*	0.63	0.08	*			
Hip Peak Absorption (W/kg)	0.77	0.05	0.58	0.04	*	0.61	0.10				
Knee Peak Extension (Nm/kg)	0.61	0.04	0.42	0.03	*	0.45	0.07	*			
Ankle Peak Plantarflexion (Nm/kg)	1.25	0.06	0.92	0.04	*	0.95	0.10	*			
Ankle Generation (W/kg)	3.94	0.23	2.39	0.18	*	2.48	0.41	*			
Absorption Energy Area (W/kg)	0.11	0.01	0.12	0.01	$\beta$	0.08	0.01	*			
Generation Energy Area (W/kg)	0.19	0.02	0.10	0.01	*	0.08	0.03	*			

**Conclusions:** Compared to the Control Group, the OI Group had several gait abnormalities that were characteristic of all OI types and which increased with severity of OI. This is an important finding as it suggests that as severity of the disease at the cellular level (which depicts OI type) worsens, not only do gait deviations common to all individuals with OI progress, but additional deviations emerge both proximally and distally.

**24. Pulmonary radio-aerosol mucociliary scan to evaluate Primary ciliary dyskinesia in children with bronchiectasis**

Hasan Ghandourah, Reza Vali, , Kimia Veisi nezhad , Yusauf Omerkheil , Afsoon Khazaei,

Martin Charron, Amer Shammam and Sharon Dell

Departments of Pediatric Respiratory Medicine, Medical Imaging and Pediatrics,

The Hospital for Sick Children, Toronto, Ontario, Canada.

Brampton nuclear service, Brampton, Ontario, Canada.

**Objectives:** The aim of our study is to determine the accuracy of PRMC test for diagnosing of PCD in children.

**Methods:** Children with suspected diagnosis of PCD underwent PRMC when standard diagnostic testing was indeterminate or not available. The scans were performed after inhalation of nebulized 99mTc Sulfur Colloid (SC) and dynamic imaging for 60-120 minutes. Migration of the radioopaque bolus from bronchi towards trachea was observed by two nuclear medicine physicians independently and classified as negative, or positive. The results were compared to two physicians' clinical diagnosis of PCD who were blinded to the result of the PRMC. The physician used the cumulative clinical history and results of all diagnostic testing performed to date to categorize the diagnosis as follows: definite PCD (classic TEM defect or biallelic mutations in a PCD causing gene), probable PCD (PCD phenotype and low nasal nitric oxide on two different occasions), indeterminate or not PCD.

**Results:** PRMC was performed on 38 patients (6-17 years of age) during a 6 years period. Six now have confirmed PCD by genetics (two CCNO and one each of DNAH11, DXY1C1, SPAG1 and DNAH5) and one by classic TEM defect. All definite PCD had positive PRMC, yielding a sensitivity and negative predictive value of 100%.

**Conclusions:** PRMC test is a non-invasive and feasible test in children with a high negative predictive value for PCD. It may be a helpful adjunctive test to rule out PCD when clinical suspicion remains after negative TEM and genetic testing.

**Table 1 PRMC results in relation to the final clinical diagnosis**

PRMC Test	Final Clinical diagnosis related to the results from the clinical diagnosis			
	Definite PCD 7 (18%)	Probable 3 (7%)	Not PCD 21 (55%)	Indeterminate 7 (18%)
Positive test	7	2	3	2
Negative test	0	1	18	5



## 25. Variation in erythrocyte and plasma protoporphyrin levels over time in protoporphyrias

Gou E<sup>1</sup>, Weng C<sup>2</sup>, Phillips JD<sup>2</sup>, Greene T<sup>2</sup>, Balwani M<sup>3</sup>, Bissell DM<sup>4</sup>, Bloomer JR<sup>5</sup>, Bonkovsky HL<sup>6</sup>, Desnick RJ<sup>3</sup>, Naik H<sup>3</sup>, Sadagoparamanujam VM<sup>1</sup>, Anderson KE<sup>1</sup>

<sup>1</sup>U of Texas Medical Branch, Galveston TX; <sup>2</sup>U of Utah, Salt Lake City, UT; <sup>3</sup>Icahn S of Med at Mt. Sinai, NY, NY;

<sup>4</sup>U of CA at San Francisco; <sup>5</sup>U of AL at Birmingham; and <sup>6</sup>Wake Forest University, Winston-Salem, NC

**Objective:** Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) cause painful, non-blistering cutaneous photosensitivity. EPP, the third most common porphyria and the most common in children, is due to decreased activity of ferrochelatase (FECH), which catalyzes the insertion of iron into protoporphyrin IX to complete heme synthesis. XLP is less common and is due to gain of function mutations of the erythroid form of  $\delta$ -aminolevulinic acid synthase, the first enzyme in the heme biosynthetic pathway. Hepatotoxic effects of excess protoporphyrin cause protoporphyrin hepatopathy in <5% of patients. Normal variability in protoporphyrin levels over time has not been characterized in EPP and XLP, and whether threshold levels lead to hepatopathy is not known.

**Methods:** Coefficients of variation (CV) were determined for levels of erythrocyte and plasma protoporphyrin repeated at least 4 times over 4 to 226 months in 92 subjects with documented EPP or XLP, after excluding those with hepatopathy or elevated transaminases.

**Results:** Total erythrocyte protoporphyrin was higher, on average, in XLP than in EPP ( $p < 0.001$ ). Total erythrocyte protoporphyrin was higher, on average, in males with XLP than females ( $p = 0.35$ ). The CV for repeated values of total erythrocyte protoporphyrin averaged 18.96, and was not significantly different in EPP and XLP (18.66 and 22.10 respectively). Variation in assay measurement accounted for less than 0.50% of total variation. Analysis on a subcohort of 27 subjects from 15 families found that 50% of variance was explained by family effect. To date, none in this cohort have developed hepatopathy or sustained upward trends in protoporphyrin levels.

**Conclusions:** Variation in erythrocyte protoporphyrin levels of up to ~25% may occur in EPP and XLP in the absence of liver disease. Assay variation has a minimal effect on longitudinal variation. Studies in more patients over longer periods of time are in progress to see if greater increases or threshold levels of erythrocyte and plasma protoporphyrin precede the development of overt protoporphyrin hepatopathy.

## 26. MEP1A mutation identified by whole exome sequencing in a family with slipped capital femoral epiphysis

Yiran Guo<sup>1</sup>, Hakon Hakonarson<sup>1,2,3</sup>

1) Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA;

2) Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA;

3) Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.

**Objective.** Slipped capital femoral epiphysis (SCFE) is an important pediatric and adolescent hip disorder in which a fracture through the growth plate (physis) results in slippage of the overlying end of the femur (epiphysis). Risk factors include sex (boy vs girl ratio around 2:1), ethnicity (Africans and Polynesians have higher rates), overweight/obesity (found in 2/3 of SCFE cases), and metabolic endocrine disorders (e.g. hypothyroidism, panhypopituitarism, hypogonadism, renal osteodystrophy, and growth hormone abnormalities). This study aims at identifying causal genes/mutations that are linked to SCFE.

**Methods.** In a family with dominantly inherited bilateral SCFE and severe obesity, we conducted whole exome sequencing in two affected kids using Agilent V5 exon capture array and Illumina HiSeq 2500 machines. After obtaining raw sequence files (fastq), we performed a series of bioinformatics processes of short read alignment to human reference genome (UCSC hg19; using BWA), variant calling (using GATK), variant annotation (using Annovar), and variant prioritization (using in-house scripts). We also validated the variants by Sanger sequencing. Functional experiments are ongoing.

**Results.** We found a missense mutation in an enzyme gene MEP1A (meprin A subunit alpha; also known as endopeptidase2, NbenzoylLtyrosylpaminobenzoic acid hydrolase, PABApeptide hydrolase, or PPH). Sanger validation showed that this mutation is shared by two affected children and their affected mother. The mutation is located at a highly conserved genomic region (astacin) across vertebrates with very deleterious predictions, and is absent from any public database including ExAC of ~60,000 samples. The human BMP1 gene (bone morphogenetic protein1) has the same domain astacin, mutations in which can cause osteogenesis imperfecta with SCFE relevant manifestations such as lack of bone modeling with wide distal metaphyses of femora. There are previous reports associating MEP1A gene variants with insulin metabolism, showing the importance of metalloendopeptidases in the breakdown of the gut hormone, and also linking metalloproteases meprin  $\alpha$  and meprin  $\beta$  which are C and Nprocollagen proteinases to collagen assembly and tensile strength. We will have functional results to characterize the role of MEP1A in developing SCFE related phenotypes.

**Conclusion.** MEP1A is a promising candidate gene linked to SCFE.

**27. The NHLBI Lymphangioleiomyomatosis Registry-Longitudinal Analysis of Pulmonary Function**

N. Gupta<sup>1</sup>, H.S. Lee<sup>2</sup>, J. Moss<sup>3</sup>, A.M. Taveira-DaSilva<sup>3</sup>, G.J. Beck<sup>4</sup>, J.H. Ryu<sup>5</sup>, F. X. McCormack<sup>1</sup>, & the NHLBI LAM Registry Group.

<sup>1</sup> University of Cincinnati, Cincinnati-OH; <sup>2</sup> University of South Florida, Tampa-FL<sup>3</sup> National Heart, Lung, and Blood Institute, Bethesda-MD; <sup>4</sup> Cleveland Clinic Foundation, Cleveland-OH; <sup>5</sup> Mayo Clinic, Rochester-MN

**Objective:** Pulmonary lymphangioleiomyomatosis (LAM) is a progressive, female-predominant, cystic lung disease that occurs both sporadically and in patients with tuberous sclerosis complex (TSC). The objective of this study was to better define the natural history of lung function decline in women with LAM.

**Methods:** Over a 3 year period (1998 – 2001), 258 patients with LAM were enrolled into an NHLBI funded registry at 6 sites around the U.S. Longitudinal data collected included serial pulmonary function measurements every six months for a period of 5 years through 2003. A longitudinal mixed effects model was analyzed with FEV<sub>1</sub> (ml) as the outcome. Modeled effects included age at enrollment ( $\leq 35$ , 36-45, 46-55, and  $> 55$ ), smoking status (current or ex, never), progesterone use (yes, no), LAM type (sporadic, TSC), and bronchodilator responsiveness (yes, no). The analyses were performed using SAS for Windows, Version 9.4, SAS Institute, Cary NC.

**Results:** A total of 258 women with a definite diagnosis of LAM were enrolled, including 213 patients with sporadic LAM and 45 with TSC associated LAM. The median age at enrollment was 44 years (range 17 – 76 years), and the median duration of follow up was 36 months (range 0 – 60 months). There were 9 current smokers, 92 ever smokers and 158 never smokers. Patients with only one measurement of their pulmonary function or lung transplantation prior to study enrollment were excluded. Mean FEV<sub>1</sub> at enrollment was 2.09 liters and the mean rate of decline for the entire cohort was  $71.78 \pm 6.7$  mls/year. Smoking ( $p=0.05$ ) and age at enrollment of  $< 55$  years ( $p=0.04$ ) were associated with a greater rate of FEV<sub>1</sub> decline. There was no significant difference in rate of decline in TSC versus sporadic LAM patients ( $p=0.14$ ,  $n = 36$  TSC, 170 sporadic-LAM).

**Conclusions:** In patients with LAM, lung function decline occurs at an accelerated rate that is influenced by baseline lung function, age and other factors. A better understanding of the natural history of LAM will facilitate clinical decision-making and the design of clinical trials.

**28. Initial Presentation of Dyskeratosis Congenita in IFIH1 Mutations With an Associated Phenotype of Aicardi Goutieres Syndrome**

S Hamoud, K Marathe, A Vanderver, S. Hufnagel, K.A. Chapman  
Children's National Health System, Washington DC

**Introduction:** Aicardi Goutières Syndrome (AGS) is a neuro-inflammatory condition associated with mutations in a series of nucleases (*TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*) or genes encoding proteins important to the interferon signaling pathways (*ADARI*, *IFIH1*). While AGS has long been known to be associated with lupus like skin findings such as chilblains, an expanding phenotypic spectrum of dermatologic abnormalities is being recognized in individuals with AGS gene related mutations. Specifically, patients with *IFIH1* mutations have been described to have psoriatic skin lesions (Marguet et al, Am J Med Genet A. 2016 May) and presentations limited to skin findings (Bursztein et al, Br J Dermatol., 2015 Dec). Of note, *IFIH1* has also been associated with a susceptibility to psoriasis (Chen et al, In J Immunogenet, 2012 Apr).

**Case Outline:** We present two patients who presented in the first 2 years of life (Patient 1 at 20 months and Patient 2 at 15 months) with failure to thrive in the context of a generalized cutaneous eruption with diffuse xerosis and reticulated hyperpigmented macules and patches with associated nail dystrophy. Initial evaluations focused on the differential diagnosis of Dyskeratosis Congenita. Over time skin findings became increasingly inflammatory in appearance with edema and tender erythematous nodules; however, the reticulated hyperpigmented lesions continued to dominate the clinical picture. A skin biopsy of one of the tender nodules several months after onset demonstrated evolution of lesions to lobular panniculitis with large vessel vasculitis. Evolution of neurologic disease over time including developmental regression, and the identification of intracranial calcifications ultimately led to a diagnosis of AGS associated with *de novo* *IFIH1* mutations in both individuals (30 months and 14 years).

**Conclusion:** This report highlights the variability of skin findings in AGS and suggests that this disorder should be considered in the differential diagnosis of an infant presenting with features suggestive of Dyskeratosis Congenita. In particular, extensive skin abnormalities in the context of neurologic regression should suggest heritable disorders of the interferon pathway, including AGS.

## 29. PKAN (Pantothenate Kinase 2-Associated Neurodegeneration) Mouse Models Showed Changes Resembling Human Patients; A New Chance for Pre-Clinical Trials

Suh Young Jeong, PhD, Jeffrey Hamada, BA, Rachel Fox, BA, Martina Ralle, PhD,  
Suzanne Mitchell, PhD, Penelope Hogarth, MD, and Susan J. Hayflick, MD.  
Oregon Health and Science University, Portland, OR, USA

**Objective** NBIA (Neurodegeneration with brain iron accumulation) is a group of devastating juvenile diseases with neurological symptoms. Although these are rare diseases, the young patients' suffering lasts decades and there are currently no therapeutics to treat the cause. Among ten subtypes, PKAN (Pantothenate kinase 2 (*Pank2*)-associated neurodegeneration) is the most common type, yet three more NBIA's are caused by genes that share biological pathways with *Pank2*. Therefore, our objective is to understand and develop models that will benefit multiple NBIA's.

**Methods** Previously, we developed *Pank2* KO mice (*Pank2*<sup>-/-</sup>), however these mice do not exhibit neurological phenotypes. In this study using *Pank2*<sup>-/-</sup> brain, we dissected out globus pallidus (GP)-enriched area where we find pathological damages in human. Combining sub-cellular fractionation and ICP-MS (Inductively coupled plasma mass spectrometry) for metal analysis, we analyzed both cytosolic and mitochondrial iron status in the *Pank2*<sup>-/-</sup> brain. We also generated a KI mouse (*Pank2*<sup>KI/KI</sup>) line, which expresses mutated *Pank2*. This mutation is equivalent to a human mutation, which causes severe early-onset PKAN in patients. In collaboration with Department of Behavioral Neuroscience at OHSU, we analyzed impulsive behavior in these mice. This behavior has been well recognized in PKAN patients.

**Results** The *Pank2*<sup>-/-</sup> GP area showed significantly increased cytosolic iron without changes in other trace metals. Interestingly, this change is not detected in other areas of the brain, indicating an area-specific vulnerability for mis-managed iron accumulation under the *Pank2* mutation. In the *Pank2*<sup>KI/KI</sup> study, our preliminary data indicate either *Pank2*<sup>KI/KI</sup> showed increased impulsive behavior or potential problems in restraining themselves from rewards. This data is still preliminary and we are currently expanding our colony.

**Conclusions** Our preliminary data indicate that both *Pank2*<sup>-/-</sup> and *Pank2*<sup>KI/KI</sup> showed interesting changes that resemble human PKAN patients compared to control mice. By dissecting the *Pank2*<sup>-/-</sup> brain into a GP-enriched area, we found significant changes that we did not detect previously using the whole brain. These data suggest that these mice might be novel models to test pre-clinical drug treatment for PKAN and other related NBIA disorders.

## 30. Assessing the Driving Ability in Those with Charcot Marie Tooth Disease Type 1A (CMT1A)

Jerath, N. et al.  
Inherited Neuropathies Consortium  
University of Iowa Carver College of Medicine, Iowa City, IA

**Background:** Driving is a complex task that requires rapid responses, which can be impaired by weakness and sensory loss. Patients with CMT1A provide a suitable cohort for a study in how peripheral neuropathy affects driver performance and safety.

**Methods:** Licensed drivers with CMT1A (n= 18; age = 42 ± 7) and controls (n=19; age = 35 ± 10) were tested using driving simulation scenarios implemented on the Simulator for Interdisciplinary Research in Ergonomics and Neuroscience (SIREN), a high performance fixed-base driving simulator. The CMT neuropathy score (CMTNSv2) was obtained on all patients with CMT1A. T-tests were used to compare driving measures. Spearman rank correlations were used to test for associations between clinical factors and the driving measures.

**Results:** Drivers with CMT1A reported similar number of motor vehicle accidents on average compared to controls. Drivers with CMT1A had 74% higher rates of lane departures and 89% higher rates of lane deviations than controls (p=0.005 and p<0.001, respectively). Lane control variability, measured by the standard deviation of lane position (SDLP), was 10% higher in the CMT group (p=0.046). The only measure of driving that was significantly correlated with the CMT neuropathy score was SDLP (r<sub>s</sub>=0.518, p=0.040). This correlation appeared to be associated with sensory leg symptoms (r<sub>s</sub>=0.710, p=0.002) and pinprick loss (r<sub>s</sub>=0.490, p=0.054).

**Conclusion:** Driving simulator-based assessments indicated drivers with CMT1A had more errors compared to control drivers. Lower extremity sensory manifestations correlated with driving errors. Future studies could be performed to investigate the use of adaptive equipment such as hand controls.

**31. Role of Oxidative Stress and Inflammation in Type 1 Gaucher Disease (GD1): Potential Use of Antioxidant/Anti-inflammatory Medications**

Reena V. Kartha<sup>1</sup>, Ghada Elnashar<sup>1</sup>, James Joers<sup>2</sup>, Paul Tuite<sup>3</sup>, Laurie Hovde<sup>1</sup>, Usha Mishra<sup>1</sup>,  
Kyle Rudser<sup>4</sup>, Gulin Oz<sup>2</sup>, Jeanine Jarnes Utz<sup>1,5</sup>, James Cloyd<sup>1</sup>

<sup>1</sup>Center for Orphan Drug Research, <sup>2</sup>Center for Magnetic Resonance Research;

<sup>3</sup>Neurology; <sup>4</sup>Biostatistics; University of Minnesota;

<sup>5</sup>UMN Medical Center/Fairview Health Systems, Minneapolis, Minnesota, United States, 55455

**Objective:** Type 1 Gaucher disease (GD1), an autosomal recessive disorder, is caused by mutations in the lysosomal enzyme gene, glucocerebrosidase (GBA). The peripheral symptoms of GD1 are well documented, but recently there is emerging recognition of neurologic involvement in these patients including association of GBA mutation with Parkinsonism. Current therapies significantly improve outcome, but patients continue to experience pain and fatigue. We hypothesize that this is due to increased oxidative stress and inflammation in GD1. Hence, adjunctive therapy with an antioxidant/anti-inflammatory agent has the potential to ameliorate ongoing symptoms. The primary objective of this project is to characterize oxidative stress and inflammation in the blood and brain of patients with GD1 who are stable on therapy and compare these biomarkers with those of healthy controls.

**Methods:** Recruitment is underway to enroll 30 adult patients with GD1 and 20 age-matched healthy individuals. The study involves 2 phases. During the baseline phase, all participants will provide 3 blood samples over 90-days for biomarker analysis in plasma/red blood cells. Subjects will also undergo a magnetic resonance spectroscopy (MRS) study at 7 Tesla for measuring neurochemical levels in regions containing cortical gray matter (posterior cingulate), white matter (occipital), and subcortical gray matter (putamen). During intervention phase, GD1 patients alone will be given 3600mg/day of oral N-acetylcysteine (NAC) for 90 days. Blood samples will be collected 3 times at monthly intervals and a second MRS study will be performed at the end of 3 months. Further, multiple blood samples will be collected at the last visit to characterize NAC and metabolite pharmacokinetics.

**Results:** We have validated our MRS, immunoassay and liquid chromatography/mass spectrometry methods and optimized sample storage conditions. Our preliminary analyses indicate less variability in glutathione redox ratio on storage at -80°C. Samples at -20°C showed ~38% and ~29% reduction in redox ratio and total glutathione, respectively. Preliminary results from neurochemical and biomarker assays will be discussed.

**Conclusions:** Our results will be used to provide guidance to clinical sites regarding sample-handling procedures to generate reproducible data on oxidative stress/inflammatory biomarkers.

### 32. A Multicenter North American Study of the Gillette FAQ in Osteogenesis Imperfecta

Kruger KM<sup>1</sup>, Caudill A<sup>2</sup>, Nagamani CS<sup>3</sup>, Smith PA<sup>2</sup>, Harris GF<sup>1,2</sup>, Members of the BBD Consortium\*

<sup>1</sup>Marquette University, Milwaukee, WI, <sup>2</sup>Shriners Hospitals for Children, Chicago, IL, <sup>3</sup>Baylor College of Medicine, Houston, TX

**Objective:** Osteogenesis imperfecta (OI) is a genetic disorder of the bones that limits ambulatory ability. To advance clinical research, the Linked Clinical Research Centers (LCRC), a network of five clinical centers in North America with significant experience in treating patients with OI, was established in 2009 as part of the Rare Diseases Clinical Research Network (RDCRN). The goal of this study was to analyze mobility to better understand the natural disease history and improve the care of patients.

**Methods:** Data analyzed included the Gillette Functional Assessment Questionnaire (FAQ) for subjects over 3 years of age. The FAQ includes a ten-level classification of ambulatory function (FAQ Walking Scale) and 22 functional locomotor activities. The FAQ is intended for use in individuals with all levels of walking ability, and focuses on what an individual can do independently with the use of assistive devices or orthoses. One way mixed factor analysis of covariance was used to determine if there were differences in the FAQ Walking Scale between various types of OI (JMP statistical software).

**Results:** From the database, 480 age 3+ were identified (average (years): 19.0±14.6, range 3.1-67.3). Subjects were identified with six OI types. The analysis revealed statistically significant differences in the FAQ Walking Scale between OI types. Selected results from the FAQ 22 question exam are included in Table 1.

**Conclusions:** The prognosis of a child with a particular type of OI is of clinical interest, particularly when setting goals for rehabilitation. Understanding disease related characteristics specific to each group allows for more accurate patient comparisons and expectations.

**Table 1:** Selected components of the FAQ. Percentage indicates participants responding yes to the question

Task	Type I	Type III	Type IV	Type V	Type VI	Type VII	Unclassified
Can take steps backward	98.1%	43.4%	73.9%	73.3%	60.0%	50.0%	44.4%
Can maneuver in tight areas	97.2%	36.1%	77.6%	73.3%	50.0%	50.0%	66.7%
Jump rope	63.0%	4.8%	23.9%	20.0%	10.0%	25.0%	11.1%
Ride 2 wheel bike	66.4%	3.6%	24.6%	20.0%	0.0%	25.0%	22.2%
Walk carrying an object	99.1%	39.8%	76.9%	73.3%	60.0%	50.0%	55.6%
Ice skate or roller skate	33.2%	2.4%	9.7%	6.7%	0.0%	0.0%	0.0%

**Acknowledgements:** The authors thank the members of the Brittle Bone Disease (BBD) Consortium\* (Brendan Lee, V. Reid Sutton, Frank Rauch, David Eyre, Francis Glorieux, Tracy Hart, Deborah Krakow, Jeffrey Krischer, Eric Orwoll, Cathleen Raggio, Jay Shapiro, Laura Tosi, Anne Tsai). The BBD Consortium (1U54AR068069-0) is a part of the RDCRN and is funded through a collaboration between the ORDR, NCATS, NIAMAS, and NIDCR. Additional funding was provided by Children's Brittle Bone Foundation, OI Foundation, and NIDLRR Grant 90AR5022-01.

**33. A Prospective, Multicenter Study to Compare and Validate Endoscopic, Histologic, Molecular, and Patient-Reported Outcomes in Patients with Eosinophilic Gastro-intestinal Diseases**

Rothenberg ME<sup>1</sup>, Kuhl JT<sup>1</sup>, Aceves SS<sup>1</sup>, Carpenter C<sup>1</sup>, Dellon ES<sup>1</sup>, Falk GW<sup>1</sup>, Gonsalves NP<sup>1</sup>, Gupta SK<sup>1</sup>, Hirano I<sup>1</sup>, Kantor S<sup>1</sup>, Leung J<sup>1</sup>, Spergel JM<sup>1</sup>, Wershil BK<sup>1</sup>, Venter C<sup>1</sup>, Furuta GT<sup>1</sup>,  
<sup>1</sup>Consortium of Eosinophilic Gastrointestinal Researchers

**Objectives:** Eosinophilic gastro-intestinal diseases (EGIDs) include Eosinophilic Esophagitis (EoE), Eosinophilic Gastritis (EG) and Eosinophilic Colitis (EC) are rare diseases in need of better understanding. The main aim of the trial is to determine clinical and pathological features of patients with EoE, EG, and EC in a cross sectional and longitudinal study. The data described below summarizes the demographics of the first 202 patients recruited into the study.

**Methods:** Recruitment started in January 2015. Patients were enrolled across the ten Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) sites in the U.S. Clinical features of subjects were determined using the REGID (Registry for Eosinophilic GI Diseases) Intake Form. Data was analyzed using descriptive statistics.

**Results:** In total, 202 participants have been recruited into the study; 178 with EoE, 14 with EG and 4 with EC. Gender per EGID diagnosis indicated a male and female proportions in EoE of 71.5 vs. 28.5%; ( $p=0.001$ ), 42.9 vs. 57.1%, ( $p=0.45$ ) for EG, 25 vs. 75%, ( $p=0.75$ ) for EC. Demographic information was available for 179 cases and demonstrated an age range of 3-62 years (mean age 22 years), male vs. female (67.6 vs. 32.4%;  $p<0.001$ ), and race (91.8% white, 5.3% African American, 1.2% Asian and 1.8% mixed races). Information on medical history was available on  $n=101$  cases. Of these, 88 reported a diagnosis of EoE only, 6 had EG only and 3 had isolated EC. Focusing on EoE, ( $n=91$ ), 40.7% ( $n=37$ ) reported to be on dual therapy (diet and steroids), 27.5% ( $n=25$ ) were on topical/oral steroids, 20.9% ( $n=19$ ) were on diet therapy and 10.9% ( $n=10$ ) listed no treatment. For EG 44.4% ( $n=9$ ) reported steroid therapy, 44.4% diet therapy and 11.1% other therapy. For EC 20% ( $n=5$ ), reported to be on dual therapy, 20% was on steroid therapy, 20% on diet therapy and 40% reported no therapy. Of those suffering from EoE, 23% (21/91) reported a history of impactions and 16.5% (15/91) had dilations in the past.

**Conclusion:** We have recruited 202 EGID participant. Diet, steroid and combination of both therapies were commonly employed. The enrichment of EoE amongst males is preliminarily not seen in EG and EC.

**34. The impact of the disease burden on the quality of life of patients with lysosomal storage disorders: preliminary data of adult patients**

Sandra Obikawa Kyosen, Erika Mitie Yamashiro Coelho, Kelin Chen, Edna Tiemi Sakata,  
Rosangela Maria da Silva, Ana Maria Martins  
Reference Center of Inborn Errors of Metabolism, Federal University of Sao Paulo

**Objective:** Lysosomal storage disorders (LSD) affect multiple systems, thus, besides the organ damage *per se*, patients present some negative impact in their quality of life (QOL). As part of the routine outcome monitoring, to evaluate the QOL of LSD patients, we use the SF-36 survey to assess functioning, and the WHOQOL-BREF to assess satisfaction/well-being in adult patients.

**Methods:** Retrospective cross-sectional study medical records of LSD patients under follow-up at a outpatient clinic part of the public health care system.

**Results:** Forty-one patients answered the surveys, but 6 were incomplete and were excluded. Of the remaining 35 patients, there were Gaucher disease ( $n=18$ ), Fabry disease ( $n=14$ ) and mucopolysaccharidosis types I ( $n=2$ ), II ( $n=3$ ) and VI ( $n=2$ ) patients, 34 of them (87%) were under enzyme replacement therapy (ERT); mean age of patients at the time of surveys completion ( $n=35$ ) and mean time under ERT ( $n=34$ ) were 35.3y (18.5y – 70.4y) and 9.1y (0.1y – 19.6y), respectively. Regarding the SF-36 survey, the mean descriptive measures of the standardized scores for the eight domains was 74.9 for physical functioning (PF), 62.1 for role-physical (AF), 64.4 for bodily pain (BP), 57 for general health (GH), 59.1 for vitality (VT), 80 for social functioning (SF), 73.3 for role-emotional (RE) and 68.5 for mental health (MH). Comparing those findings to the Brazilian normative data, the patients scored below to the average Brazilian age-matched counterparts in PF, AF, P, GH and VT; almost the same in SF and RE and scored higher in MH. Regarding WHOQOL-BREF survey, each domain scores from 1 to 5 on a Likert scale, the scores are then transformed into a linear scale between 0 and 100, being 0 the least and 100 the most favorable QOL. The mean scores of our patients on the four domains were 64.7 for physical, 72.7 for psychological, 72.2 for social and 61.7 for environment. Unfortunately, we do not have WHOQOL-BREF normative data for Brazilian population.

**Conclusions:** In our sample, it seems that the disease negatively affected the patients' QOL, and more studies are needed to measure the burden of illness on them.

**35. Evidence of multiple carboxylase deficiency in children with mutations in *MT-ATP6***

Austin A. Larson,<sup>1</sup> Shanti Balasubramaniam,<sup>2</sup> John Christodoulou,<sup>3</sup> George A. Diaz,<sup>4</sup> Emma Glamuzina,<sup>5</sup> Natalie Hauser,

<sup>6</sup>Bryce Heese,<sup>7</sup> Gabriella Horvath,<sup>8</sup> Andre Mattman,<sup>8</sup> S. Lane Rutledge,<sup>10</sup> Clara Van Karnebeek,

<sup>8</sup>Amy Williamson,<sup>4</sup> Johan K. L. Van Hove,<sup>1</sup> James D. Weisfeld-Adams<sup>1</sup>

<sup>1</sup>University of Colorado School of Medicine, Aurora, CO;

<sup>2</sup>Princess Margaret Hospital, Perth, Australia;

<sup>3</sup>University of Melbourne, Melbourne, Australia;

<sup>4</sup>Icahn School of Medicine at Mount Sinai, New York, NY;

<sup>5</sup>Starship Children's Hospital, Auckland, New Zealand;

<sup>6</sup>Valley Children's Hospital, Madera, CA;

<sup>7</sup>University of Missouri-Kansas City School of Medicine, Kansas City, MO;

<sup>8</sup>University of British Columbia, Vancouver, Canada;

<sup>9</sup>University of Alabama at Birmingham, Birmingham, AL

**Objective:** To report a newly-identified association of multiple carboxylase deficiency with mutations in *MT-ATP6*.

**Methods:** Retrospective chart review for patients with *MT-ATP6* mutations and biochemical evidence of multiple carboxylase deficiency.

**Results:** Eight individuals with abnormal acylcarnitine profile suggestive of multiple carboxylase dysfunction were found to have mutations in *MT-ATP6*, namely m.8993T>G in six patients (all at least 87% heteroplasmy in blood), m.9176T>G in one patient (homoplasmic in blood) and two novel but likely pathogenic variants in one patient. Most were initially ascertained with abnormal newborn screening through tandem mass spectrometry. All had normal enzymatic or molecular genetic testing to exclude biotinidase and holocarboxylase synthetase deficiencies. All patients were treated with supplemental biotin, 7/8 showed no biochemical response. Clinical outcomes ranged from death in early childhood due to neurodegenerative disease to clinically asymptomatic with normal development over five years of follow-up. Five patients had serum amino acid concentrations measured and all had low citrulline.

**Conclusions:** These cases expand the biochemical phenotype associated with *MT-ATP6* mutations, especially m.8993T>G, to include multiple carboxylase deficiency. Clinicians should be aware of the association and its implications for newborn screening follow-up and consider mtDNA sequencing for patients with combined elevations of C3 and C5OH acylcarnitines in whom biotinidase and holocarboxylase synthetase deficiencies have been excluded.

### 36. Diagnostic Delays in Rare Disease: Identifying Factors and Developing Strategies to Address

Latino GA, Kim H, McCulloch C, Faughnan ME, and the Brain Vascular Malformation Consortium HHT Investigator Group

1) Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada

2) Division of Respiriology and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada

3) Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care,

University of California, San Francisco, USA

4) Institute for Human Genetics, University of California, San Francisco, USA

**Objectives:** Using expert opinion to determine the factors influencing timely recognition of Hereditary Hemorrhagic Telangiectasia (HHT), as the first step in a multi-stage project aiming to address the issue of diagnostic delay in HHT and rare diseases in general.

**Methods:** A brief electronic survey was developed asking experts for their opinion on three factors that contribute to both delayed and timely diagnosis in patients with HHT. The survey was sent to the 32 HHT Center Directors and Brain Vascular Malformation Consortium members across North America. Responses were coded and frequency calculated to determine the most commonly suspected reasons for delayed and timely diagnosis.

**Results:** A total of 22/32 (69%) individuals completed the survey, the majority of whom practiced in the United States (31/32 or 97%) and all practised in academic center (32/32 or 100%). A summary of their responses may be found in Table 1.

**Table 1: Expert opinion on the factors influencing timeliness of diagnosis in HHT**

<b>Factors contributing to DELAYED diagnosis in HHT</b>	<b>Frequency n=22</b>
Lack of awareness of disease and diagnostic criteria by physicians	72%
Patient denial of diagnosis and reluctance to get screened	45%
Asymptomatic or mild disease symptomatology	41%
Lack of awareness of disease by patients, public and media	36%
No local expertise or lack of access to resources	32%
Diagnostic overlap with common diseases, misdiagnosis and diagnostic anchoring	27%
Misperception of the importance of early diagnosis and screening	18%
<b>Factors contributing to TIMELY diagnosis in HHT</b>	<b>Frequency n=22</b>
Access to local expertise and resources (including genetic testing)	55%
Increased local physician education and awareness of disease	55%
Family member diagnosed with disease and advocacy for other relatives to be tested	45%
Access to internet and effective use of available search engines by patients and physicians	32%
Presence of classic symptoms, severe symptoms or disease-related complications	27%
National and international awareness campaigns by HHT Foundation, experts and patients	27%
Increased local patient and public education and awareness of disease	18%

**Conclusions:** We have identified several potential targets to improve diagnosis in HHT. The results of this study will be used to guide future questionnaires and inform the next steps of our project, which includes: understanding the patient perspective and experience with diagnostic delay; assessing how various multi-disciplinary diagnostic centers address the factors influencing timely diagnosis; and developing local strategies that may be adopted broadly to increase the diagnosis and recognition of rare disease.



### 37. Whole exome sequencing identifies genes converge on PI3K/mTOR and Ras/MAPK pathways as causes of generalized lymphatic anomaly

Dong Li<sup>1</sup>, Tara L. Wenger<sup>2</sup>, Michael March<sup>1</sup>, Christoph Seiler<sup>3</sup>, Alvaro Gutierrez-Uzquiza<sup>1</sup>, Lifeng Tian<sup>1</sup>, Charly Kao<sup>1</sup>, Rahul Pandey<sup>1</sup>, Kenny Nguyen<sup>1</sup>, Rosetta Chiavacci<sup>1</sup>, Patrick Sleiman<sup>1,4</sup>, Maxim Itkin<sup>5</sup>, Yoav Dori<sup>5</sup>, Hakon Hakonarson<sup>1,4,6</sup>

1. Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA, 2. Division of Craniofacial Medicine, Seattle Children's Hospital, Seattle, WA, 3. Zebrafish core, The Children's Hospital of Philadelphia, Philadelphia, PA, 4. Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, 5. Center for Lymphatic Imaging and Interventions, The Children's Hospital of Philadelphia, Philadelphia, PA, 6. Divisions of Genetics and Pulmonary Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA

**Objective:** To identify the underlying genetic basis for generalized lymphatic anomaly (GLA).

**Methods:** Exome sequencing (ES) was performed in four families, including a multigenerational family (family-1) with six affected members. RNA-seq was performed on skin biopsies obtained from the lead proband in family-1. We used zebrafish model to understand the roles of the mutated genes, *EPHB4*, *PIK3R6* and *ARAF* in vascular morphogenesis.

**Results:** In family-1, 6 affected individuals in multigenerational were revealed to have heterozygous *EPHB4* mutation (c.2334+1G>C), a gene previously implicated in a biological pathway related to venous and lymphatic cell fate determination. RNA-seq demonstrated that the *EPHB4* splice-altering mutation creates a cryptic splice donor that causes the retention of the intervening 12 bp of the intron. For family-2, ES revealed a homozygous variant, c.1393-7C>T, in *PIK3R6* in the proband with both parents being heterozygous. *PIK3R6* is a regulatory subunit of PI3K complex. Zebrafish knockdown of either *EPHB4* or *PIK3R6* resulted in vessel misbranching and deformities in the lymphatic vessel development, indicative of possibly differentiation defects both in blood and lymphatic vessels and mimicking the presentations of the patients. Western blot analysis using zebrafish lysates, which contained vascular abnormality, confirmed that reduced *EPHB4*/*PIK3R6* signaling resulted in downstream mTORC1 overactivation. Strikingly, drugs that inhibit mTOR signaling were able to rescue this misbranching phenotype. In family 3 and 4, a recurrent *de novo* *ARAF* mutation, c.640T>C:p.S214P, in the conserved phosphorylation site was identified. Overexpression of the mutant *ARAF* results in lymphatic misbranching phenotype.

**Conclusions:** We report three novel genes that converge on PI3K/mTOR and Ras/MAPK pathways that underlie GLA, presenting a potential avenue for therapeutic intervention for GLA patients.

### 38. Persistent transaminitis and dyslipidemia in a boy due to lysosomal acid lipase deficiency and response to enzyme replacement therapy.

Mari Mori, Basavaraj M Kerur, Neal LeLeiko, Chanika Phornphutkul

Hasbro Children's Hospital, The Warren Alpert Medical School of Brown University, Providence, RI

**Objective:** Lysosomal acid lipase deficiency (LALD) is an under-recognized lysosomal storage disease that leads to lysosomal accumulation of cholesteryl ester and triglycerides in liver, spleen, and other organs, resulting in hepatosplenomegaly, cirrhosis, and end-state liver disease requiring liver transplantation. Dyslipidemia in LALD is associated with accelerated atherosclerosis and cardiovascular events. Historically, severe cases were recognized as Wolman's disease presenting with infantile-onset malabsorption and rapid progression of liver failure leading to death by 6 months of age. Over the years, the spectrum of LALD has been described. Enzyme replacement therapy (ERT) with sebelipase alfa, shown to achieve normalization of transaminases, improvement of dyslipidemia and reduction of hepatic fat contents in LALD, was approved as a therapeutic option in 2015. Here, we describe an effect of ERT in a childhood-onset of LALD.

**Methods:** Case description of LALD and biochemical response to ERT.

**Results:** A five-year-old developmentally normal boy presented with acute abdominal pain. He had normal body mass index of 16.4 kg/m<sup>2</sup>. Abdominal X-ray revealed splenic silhouette concerning for splenomegaly. Splenomegaly and persistent mild transaminitis without cholestasis after the resolution of abdominal pain prompted further work-up. Doppler studies of the liver ruled out portal hypertension and biliary dilation. Abdominal MRCP revealed subtle loss of hepatic signals suggestive of mild steatosis without obvious signs of storage disorder. LALD was suspected due to the steatosis in a child with normal BMI. LAL enzyme activity on blood spot was undetectable. The diagnosis was confirmed by Sanger sequencing of the *LIPA* gene which showed compound heterozygous pathogenic variants; a previously-reported exon-skipping variant c.894G>A and a novel splice site variant c.967-1G>A. Liver biopsy, obtained to rule out other metabolic conditions, showed microvesicular steatosis along with macrophages with foamy cell changes. The patient was started on ERT, and his liver enzymes normalized and dyslipidemia improved when measured three months later. He is tolerating the ERT without side effects.

**Conclusion:** Diagnosing LALD remains challenging as it can be clinically asymptomatic unless transaminitis, dyslipidemia, or splenomegaly is incidentally uncovered. This treatable condition should not be missed in a work-up of steatosis in children or adults with normal BMI. Long-term follow-up is required to determine the ERT effect on cirrhosis and atherosclerotic processes.

**39. Esophageal Distensibility Provides Measure of Remodeling in Pediatric Eosinophilic Esophagitis**

Amanda Muir<sup>1</sup>, Alain Benitez<sup>1</sup>, Ritu Verma<sup>1</sup>, Chris Liacouras<sup>1</sup>, Robert Kramer<sup>2</sup>,  
Jonathan Spergel<sup>1</sup>, Glenn Furuta<sup>2</sup>, Calies Menard-Katcher<sup>2</sup>

<sup>1</sup>The Children's Hospital of Philadelphia

<sup>2</sup>Children's Hospital Colorado

**Objective:** Sequelae of eosinophilic esophagitis (EoE) include repeated food impactions and esophageal strictures. Duration of inflammation is currently seen as the dominant risk factor; however development of complications remains unpredictable. Functional endoLuminal Imaging Probe (EndoFLIP) has been used in adults to measure esophageal distensibility; EoE subjects had altered distensibility that associated with risk of food impaction. Given uncertainty around the natural history of EoE, assessing distensibility as a surrogate for remodeling across ages is important. We used EndoFLIP in children with EoE to predict disease activity and fibrostenosis, and we hypothesize distensibility is reduced during active inflammation.

**Methods:** Patients age 3-18 years old (y/o) undergoing endoscopy at 2 tertiary care sites were prospectively studied. Subjects: 1. Active EoE—>15 eosinophils per hpf; 2. Inactive EoE— <15 eos/hpf; 3. Controls—no esophageal inflammation and normal biopsies. EoE patients were on twice-daily proton pump inhibitor for at least 6 weeks prior to endoscopy. EndoFLIP: Following inspection, the EndoFLIP (Crospon) was positioned and the balloon inflated to luminal pressure of 50 mmHg. Analysis: Data was filtered to minimize distortion and pressure-geometry measurements were analyzed. Distensibility was determined based on minimum cross sectional area (CSA) at a luminal pressure of 40 mmHg. Outcome measures were compared between age balanced groups using t-tests or chi-square.

**Results:** 134 patients (mean age 12.24 y/o, 76% male, 84% Caucasian) were enrolled; including 46 controls, 44 active and 44 inactive, with no significant difference in mean age between groups. Distensibility was positively associated with age in controls ( $R^2$  0.604,  $p < 0.001$ ). EoE subjects had decreased distensibility compared to controls ( $p = 0.001$ ). Older EoE subjects (13-18 y/o) with active inflammation had decreased distensibility compared to age balanced inactive EoE subjects ( $p = 0.01$ ); however there was no significant difference between active and inactive younger (8-12 y/o) EoE subjects. History of impaction and stricture were both associated with decreased distensibility compared to age balanced EoE.

**Conclusion:** Children with EoE have a less distensible esophagus than controls. This difference is amplified by active disease in older subjects and in those with significant remodeling. We propose EndoFLIP will provide insights in the pathophysiology of EoE and identify patients at risk for impaction and stricture.

**40. Nutrient intake in children with Smith-Lemli-Opitz syndrome**

Semone B. Myrie<sup>1</sup>, Kate Haas<sup>2</sup>, Forbes D. Porter<sup>3</sup>, James Heubi<sup>4</sup>, Robert D. Steiner<sup>5</sup>, Peter H. Jones<sup>1</sup>, Jean-Baptiste Rouillet<sup>2,6</sup>

<sup>1</sup>University of Manitoba, Winnipeg, MB, Canada, <sup>2</sup>Oregon Health & Science University, Portland, OR, USA;

<sup>3</sup>The Eunice Kennedy Shriver National Institute of Child Health & Development, Bethesda, MD, USA;

<sup>4</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA;

<sup>5</sup>University of Wisconsin School of Medicine and Public Health, Madison, WI, USA;

<sup>6</sup>College of Pharmacy, Washington State University, Spokane, WA, USA.

**Background & Objectives:** Smith-Lemli-Opitz syndrome (SLOS) is an inborn error of cholesterol metabolism caused by mutations in 7-dehydrocholesterol reductase (*DHCR7*) gene. Patients present with multiple anomalies including feeding difficulties, and failure to thrive is common. However, systematic studies of nutrition provisions in SLOS are lacking. This study aims to provide an overview of nutrient intakes in SLOS patients in relation to dietary recommendations.

**Methods:** Three 24-hr dietary recalls were performed over 1 year in 26 SLOS patients (13/13 male/female; 1-21 years old). Seventeen patients were oral feeders (O), 4 were gastrostomy-fed (G), and 5 used both feeding methods (OG). Daily nutrient intakes were calculated using Nutrition-Data-System Research software and analyzed adjusting for age, body weight or caloric intake when appropriate.

**Results:** Average caloric intake was 75 cal/day/kg (40%/45%/15% fat/carbohydrates/proteins), similar in all 3 groups and ~16% higher than the recommended intake for healthy children. The intake of minerals, B vitamins, and antioxidants (selenium, vitamins A, C and E) was lower in O than in G or OG patients but overall exceeded daily recommended intake (from 114% to 416%). Cholesterol intake (mg/kg/day) was significantly higher in OG patients ( $36 \pm 3$ ) than in O ( $29 \pm 2$ ) or G ( $24 \pm 4$ ) patients.

**Conclusions:** This is the first controlled systematic evaluation of nutrition in SLOS. The data provide a basis for examining nutrition-clinical outcomes relationships and suggest that in SLOS failure to thrive is not the consequence of nutritional deficiency.

#### 41. FVII deficiency: Studies of the Natural History, Genotype-Phenotype Correlations, and Opportunities for Therapeutic Intervention.

Danielle Nance, MD, Arizona Bleeding Disorders Health and Wellness Center

**Abstract:** Patients with congenital FVII deficiency have variable bleeding phenotypes, which are not predicted by the absolute FVII activity level (FVII:C), nor apparently solely by genotype[1-3]. The discrepancy complicates clinical management and hampers the development of standard approaches to prevention of bleeding episodes and optimal treatment. This variability is seen among kindred and unrelated individuals with the same genotype. The underlying genotype/phenotype relationship follows some patterns seen in other factor deficiencies, but null mutations or mutations that completely interrupt gene function are rare in FVII, correlating with the hypothesis that complete absence of the FVII protein may be incompatible with life. Most mutations instead are point mutations that interrupt the co-factor function which loosely correlates with severe, moderate or mild disease. Unlike FIX deficiency, a coagulation factor with similar size and shape, and where activity levels are predictive of need for replacement therapy, patients with FVII deficiency experience marked variability in bleeding phenotypes at the same FVII activity level. This poster presents the results of an anonymous survey of 36 patients at a 2014 FVII deficient patient retreat.

**Results:** 36 patients attended a patient educational retreat and all patients were offered an anonymous survey to identify educational needs and gaps as part of the program. The survey asked about self-identified disease severity, bleeding symptoms, and treatments that had been used by attendees. Of 36 attendees, 12 identified their bleeding disorder as severe, and their self-reported factor levels varied between <1% (9 of 12) to <50% (3 of 12). Of 11 attendees with self-reported moderate disease, factor levels were <20% (5 of 10), less than 50% (3 of 10) and 3 did not know. All 36 attendees reported at least 1 bleeding symptom of concern to a health care provider, and 23 of 36 (64%) attendees reported a history of joint bleeding into at least one large joint. The frequency of bleeding symptoms reported by attendees in this survey is greater than previously published reports.[4]

**Future Directions:** the results of this survey suggest that bleeding frequency is higher than previously published reports. Further studies to accurately correlate factor levels, bleeding symptoms and genotype are needed to enable rational and directed approaches to developing therapy regimens.

##### References:

1. McVey, J.H., et al., *Factor VII deficiency and the FVII mutation database*. Hum Mutat, 2001. **17**(1): p. 3-17.
2. Herrmann, F.H., et al., *Factor VII deficiency: clinical manifestation of 717 subjects from Europe and Latin America with mutations in the factor 7 gene*. Haemophilia : the official journal of the World Federation of Hemophilia, 2009. **15**(1): p. 267-80.
3. Bernardi, F., et al., *Major differences in bleeding symptoms between factor VII deficiency and hemophilia B*. Journal of thrombosis and haemostasis : JTH, 2009. **7**(5): p. 774-9.
4. Palla, R., F. Peyvandi, and A.D. Shapiro, *Rare bleeding disorders: diagnosis and treatment*. Blood, 2015. **125**(13): p. 2052-61.

#### 42. Descriptive analysis of gut microbiome alterations in hyperoxaluric patients

Lama Nazzal<sup>1</sup>, David S. Goldfarb<sup>1</sup>, John Lieske<sup>2</sup>, Dawn Milliner<sup>2</sup>, Martin Blaser<sup>1</sup>.

1. New York University School of Medicine, New York.
2. Mayo Clinics, Rochester, Minnesota.

We will characterize the microbiome in 4 groups of subjects (primary hyperoxaluria type I (PH1), idiopathic CaOx stone, enteric hyperoxaluria (EH) and healthy participants) by comparing the number of species and diversity of the microbial populations and pathway for oxalate metabolism by paralleling the gene expression of enzymes involved in oxalate degradation by gut bacteria. We will also examine the anaerobic oxalate-degrading bacterium *Oxalobacter formigenes* (OF) and its metabolic capacity to degrade oxalate in patients with primary hyperoxaluria and healthy participants.

Kidney stones are a disease of worldwide prevalence with significant public health implications. About 60–80% of stones are composed of calcium oxalate (CaOx) for which high urinary oxalate, hyperoxaluria, is a major risk factor. Calcium and oxalate are components of the urine that can crystallize, and form CaOx kidney stones. Though oxalate is regarded as a highly toxic molecule, human cells lack the enzymes to metabolize it. Mammals harnessed colonies of bacteria that have the ability to degrade oxalate.

In a cross-sectional and observational study we will continue collecting stool specimens from patients with primary hyperoxaluria type I, idiopathic CaOx stones, enteric hyperoxaluria and healthy participants. We will review the charts of the recruited patients with primary, enteric and idiopathic CaOx stones to collect their 24-hour urine parameters to use in our analyses. Participants will also fill out a food frequency questionnaire about their dietary intake. Each group will include 15 adult participants.

We will compare the different groups tested, using data generated by 16S rRNA sequencing, for microbiome diversity and abundance of operational taxonomic units. Genome shotgun sequencing will yield comparative expression of the oxalate metabolism genes, and we will also measure oxalate degradation potential and antibiotic resistance of OF strains isolated from PH1 patients and normal controls. To date, we have enrolled 12 CaOx (11 at NYU and 1 at Mayo), 2 PH1, 2 EH and 2 healthy participants. The mean age is 43.1 ± 11.8 years and the male/female ratio is 6/12.

Finally, findings from this pilot project will improve our insights into the metabolic role of the gut microbiome, particularly OF, in hyperoxaluric conditions.

**43. Extra-Pulmonary Morbidity in a Rare Lung Disease: Growth and Developmental Impacts in Neuroendocrine Cell Hyperplasia of Infancy (NEHI)**

Rebekah J. Nevel, Errine Garnett, Abigail Arkon, Na Liu, and Lisa R. Young  
Division of Pediatric Pulmonary Medicine, Vanderbilt University Medical Center

**Objective:** Neuroendocrine cell hyperplasia of infancy (NEHI) is a rare diffuse lung disease which typically presents in the first year of life with tachypnea, retractions, and hypoxemia. Some infants present with failure to thrive (FTT), yet the frequency of this and other non-respiratory phenotypic features have not been delineated. Treatment remains limited to supportive care. While gradual improvement occurs over years, the clinical course is highly variable and supplemental oxygen requirement and PFT abnormalities persist into adolescence and adulthood in some cases. Our objective is to identify factors and comorbidities in NEHI that may drive differences in clinical course.

**Methods:** An electronic questionnaire evaluating health status was distributed to the parents/guardians of children with NEHI as part of an ongoing prospective study. Diagnostic criteria and other clinical data were obtained by chart review.

**Results:** Data were analyzed from 43 children with NEHI. The parental survey response rate was 78%. During the first year of life, 83% of children had at least 1 hospitalization and 43% of children had four or more hospitalization events. Developmental delays were noted in medical records of 30% of subjects, with ongoing concerns reported by 16% of survey respondents. 82% had a diagnosis of FTT in their medical record, with median weight percentile at initial presentation of 5<sup>th</sup> percentile (95% confidence interval, 3-17). 95% of subjects required supplemental oxygen. In subjects requiring continuous supplemental oxygen, having a diagnosis of FTT was associated with longer duration of 24 hour/day supplemental oxygen use.

**Conclusions:** NEHI is associated with substantial morbidity including requirement for supplemental oxygen and frequent hospitalizations. FTT is common in NEHI and may be associated with greater respiratory morbidity, though further studies are required to define this interaction. Developmental delays were noted in this cohort, though the domains and severity have not been systematically characterized. These data highlight the need for focused prospective data collection on growth and developmental milestones. Determining the association of these comorbidities and respiratory course in NEHI may allow for understanding of clinical variability and enable development of strategies to improve these modifiable factors and potentially pulmonary outcomes.

#### 44. Characterization of Idiopathic Bronchiectasis in Patients with and without Pulmonary Nontuberculous Mycobacterial Disease

J.A. Nguyen,<sup>1</sup> D.R. Prevots,<sup>2</sup> J. Adjemian,<sup>2,3</sup> Y. Lai,<sup>2</sup> C.M. Henderson,<sup>4</sup> M.L.A. Daniels,<sup>5</sup> M.R. Knowles,<sup>5</sup> C. L. Daley,<sup>6</sup> K.N. Olivier<sup>1</sup>

<sup>1</sup>National Heart, Lung, and Blood Institute - Bethesda, MD/US, <sup>2</sup>National Institute of Allergy and Infectious Diseases - Bethesda, <sup>3</sup>United States Public Health Service, Commissioned Corps – Rockville, MD/US, <sup>4</sup>National Institutes of Health Clinical Center - Bethesda, MD/US, <sup>5</sup>University of North Carolina - Chapel Hill/US, <sup>6</sup>National Jewish Health - Denver/US; Genetic Diseases of Mucociliary Clearance Consortium

**Objective:** Bronchiectasis has been reported more commonly in postmenopausal women with a tall, thin body morphotype and associated with pectus abnormalities, scoliosis, and nontuberculous mycobacterial (NTM) pulmonary infection. The link between bronchiectasis and these traits remains unclear. This report from the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) idiopathic bronchiectasis study explores the clinical, radiological, and microbiological relationships.

**Methods:** We conducted an interim review of the GDMCC idiopathic bronchiectasis cross sectional study. Patients with known causes of bronchiectasis or a significant smoking history were excluded. Patients were stratified at enrollment based on gender and presence/absence of NTM and then completed a single clinical visit.

**Results:** NTM women tend to be diagnosed at a younger age, have a lower FEV1% predicted and lower BMI than NTM men. Non-NTM women tend to have a higher incidence of scoliosis than non-NTM men. NTM women were older at age of diagnosis than non-NTM women. NTM women had a lower BMI than non-NTM women. NTM men were older at age of diagnosis, have a higher FEV1% predicted and a higher incidence of scoliosis than non-NTM men (Table 1).

**Conclusions:** This study suggests significant differences between NTM and non-NTM patients. These results may provide insight into underlying pathogenesis and genetic associations which require further investigation.

Table 1: Prevalence of Reported Traits

	With NTM (n=128)			Without NTM (n=127)		
	Total (n=128)	Women (n=68)	Men (n=60)	Total (n=127)	Women (n=66)	Men (n=61)
Age at Diagnosis years (mean, SD)	55 (± 17) §	53 (± 17) ° *	58 (± 16) °	44 (± 20)	44 (± 19)	43 (± 21)
Age at Enrollment years (mean, SD)	63 (± 14) §	61 (± 13) *	64 (± 14) °	55 (± 18)	57 (± 17)	52 (± 19)
FEV1 % predicted (mean, SD)	76 (± 21) §	72 (± 18) °	80 (± 23) *	68 (± 25)	69 (± 24)	68 (± 25)
nNO nL/min (mean, SD)	242 (± 110)	242 (± 93)	242 (± 130)	246 (± 117)	231 (± 92)	264 (± 140)
BMI kg/m <sup>2</sup> (mean, SD)	22.8 (± 4.3) §	22.0 (± 3.2) ° *	23.8 (± 5.2)	24.3 (± 5.3)	23.9 (± 6.1)	24.7 (± 4.2)
Scoliosis (n, % present)	61 (48%) §	35 (51%)	26 (43%) *	38 (30%)	26 (39%) °	12 (20%)
Pectus Abnormalities (n, % present)	16 (13%)	11 (16%)	5 (8%)	18 (14%)	10 (15%)	8 (13%)

Estimated prevalence and averages in the general population: Scoliosis: 1.9% (Shands AR, 1955). Pectus Excavatum: <1% (Clark JB, 1962). BMI (females): 28 (NHANES, 2004). BMI (males): 28 (NHANES, 2004); nNO = nasal nitric oxide production

§ Indicates a statistically significant value when comparing total patients with and without NTM

° Indicates a statistically significant value when comparing patients by gender within an NTM group

\* Indicates a statistically significant value when comparing patients with/without NTM within gender group

p-values: ■ <0.05, ■ <0.01, ■ <0.0001

Supported in part by Division of Intramural Research, NHLBI, NIAID, NIH and by NIH 5 U54 HL096458-09 funded by the Office of Rare Diseases Research (ORDR), and administered by NHLBI.

**45. Psychosocial predictors of depression in people with mast cell disorders**Jennifer Nicoloro-SantaBarbara<sup>1</sup>, Marci Lobel<sup>1</sup>, David Wolfe<sup>2</sup><sup>1</sup> Department of Psychology, Stony Brook University, Stony Brook, New York, USA, <sup>2</sup> Division of Medical Psychiatry, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

**Objective:** Mast cell disorders are rare, chronic illnesses that can involve cutaneous, gastrointestinal, skeletal, and cardiovascular symptoms ranging in severity, location, duration, and frequency within and across affected individuals (Castells, 2004). Monitoring and managing symptoms is an overwhelming task for many with these disorders (O'Neill & Morrow, 2001). People often suffer for years with unidentified disease, are misdiagnosed, and see a number of physicians prior to receiving an accurate diagnosis. The debilitating profile of mast cell disorders as described in the existing medical literature underscores the need for psychosocial research on individuals affected by these disorders. The purpose of the present study was to assess the prevalence of depression in a sample of patients with mast cell disorders, and to examine associations of disease impact, resilience, and coping with depression using psychometrically robust measures and methods, including some measurement tools developed specifically for this population.

**Methods:** Solicitations were emailed to members of a national organization for individuals with mast cell disorders and those listed in the Brigham and Women's Hospital Mastocytosis Registry inviting individuals 18 or older to complete an anonymous, Internet-based survey about the psychological impact of having a mast cell disorder.

**Results:** Almost two-thirds of participants (N=180) experienced clinically meaningful depression symptoms as indicated by their scores on the Center for Epidemiologic Studies Depression Scale. Depressed mood was associated with somatic symptomatology, poorer quality of life, lower resilience, and indirectly with several ways of coping. Newly-developed measures for this population assessing Quality of Life, Disease-Related Distress, and Resilience performed well psychometrically. Women reported greater use of several ways of coping, greater disease-related distress, poorer quality of life, and more symptoms.

**Conclusions:** This is one of the first scientifically rigorous investigations of factors associated with depression in individuals with this rare, chronic disease. Results confirm that depressed mood is common in this population and that it is associated with extent of symptomatology as well as by poorer quality of life, maladaptive coping, and related psychosocial factors. Study findings underscore the urgent need for further psychological research and development of effective psychosocial treatments for this population.

**46. ZFN-mediated liver-targeting gene therapy corrects systemic and neurological diseases of mucopolysaccharidosis type I**Li Ou<sup>1</sup>, Russell DeKolver<sup>2</sup>, Susan Tom<sup>2</sup>, Robert Radeke<sup>2</sup>, Michelle Rohde<sup>2</sup>, Amy Manning-Bog<sup>2</sup>, Scott Sproul<sup>2</sup>,Michael J Przybilla<sup>3</sup>, Brenda L Koniar<sup>1</sup>, Kelly Podetz-Pedersen<sup>3</sup>, Kanut Laoharawee<sup>3</sup>,Renee D Cooksley<sup>1</sup>, Michael C Holmes<sup>2</sup>, Thomas Wechsler<sup>2</sup>, R Scott McIvor<sup>3</sup>, Chester B Whitley<sup>1</sup><sup>1</sup>Gene Therapy Center, Department of Pediatrics, University of Minnesota, Minneapolis, MN,<sup>2</sup> Sangamo BioSciences, Inc. 501 Canal Boulevard, Richmond, CA, <sup>3</sup> Department of Genetics,

Cell Biology and Development, University of Minnesota, Minneapolis, MN.

**Objective:** Mucopolysaccharidosis type I (MPS I) is characterized by progressive neurodegeneration, and premature death (<10 years). Caused by  $\alpha$ -L-iduronidase (IDUA) deficiency and systemic accumulation of glycosaminoglycans (GAG), current therapies include stem cell transplant (with significant risk of morbidity and mortality), and enzyme replacement therapy (requiring costly and frequent long therapeutic infusion sessions). A promising alternative is genome editing by integration of a therapeutic hIDUA transgene using zinc finger nucleases (ZFN).

**Methods:** MPS I mice (n=8 per gender, 4-9 weeks old) were injected with a single dose of AAV2/8 encoding albumin-targeted ZFN and a donor encoding a partial hIDUA cDNA.

**Results:** MiSeq analysis showed that treated mice displayed significant levels of insertions/deletions (indels) (up to 56%) at the target locus, demonstrating efficient delivery and expression of the albumin ZFNs. Significant plasma IDUA activity was also observed in the ZFN+hIDUA donor treated mice, up to 10-fold of wildtype levels, throughout the 120-day study. Urine GAG levels serving as a biomarker for hIDUA activity were reduced significantly (up to 90%). IDUA levels in these animals increased significantly in liver (up to 14 fold), heart, lung, muscle and spleen. Tissue GAG levels were significantly reduced in liver (by 91%), heart (85%), lung (86%), muscle (68%) and spleen (84%). Barnes maze tests at the end of the study showed that ZFN+hIDUA donor treated MPS I mice achieved significant neurological benefits compared with untreated MPS I mice.

**Conclusions:** ZFN-mediated genome editing of hepatocytes *in vivo* thus resulted in high and stable levels of hIDUA expression in treated animals. This enzyme was secreted into plasma and then taken up by secondary tissues, leading to significant GAG reduction. The correction of the observable neurological impairment in MPS I mice suggests that a small but sufficient amount of hIDUA protein crossed the blood-brain barrier in these animals. The study provides a general "proof-of-concept" for treatment of lysosomal diseases.



#### 47. Defining disease subtypes in pediatric pulmonary hypertension: A network approach

Mei-Sing Ong, Kenneth Mandl

Boston Children's Hospital, Harvard Medical School

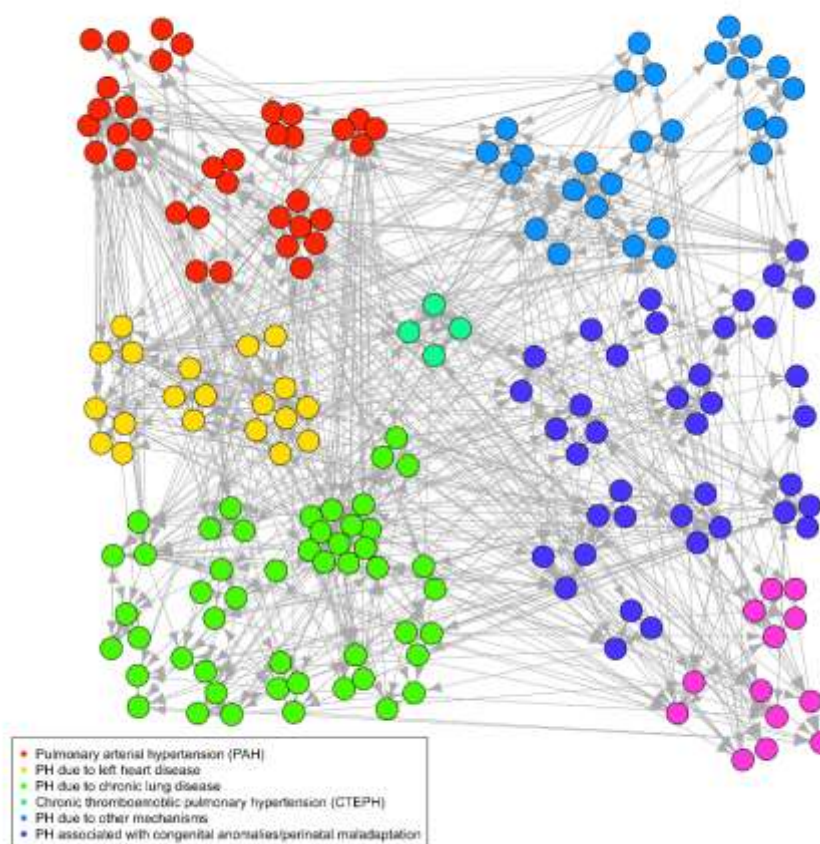
**Objective:** Pulmonary hypertension (PH) is a rare and often fatal condition characterized by increased pressure in the pulmonary circulation. Despite recent advances in treatment, survival of PH patients remains poor. Effective management relies on precise diagnosis of PH subtypes according to its underlying pathophysiology. We sought to enrich the current classifications of PH, and to facilitate the rapid discovery of novel subtypes, applying network science to the largest dataset of pediatric PH to our knowledge.

**Methods:** This is a retrospective study using un-identifiable member claims data from Aetna, a major nation-wide health insurance plan in the US (years 2010 to May 2013). Subjects included 1,583 children with PH, and 6,941,680 children without PH that formed the control population. Comorbidities significantly associated with PH were identified, and a Bayesian network was developed to characterize their inter-dependencies. Cluster analysis was then used to partition the network into subgraphs comprising comorbidities that were highly connected. The resulting network-derived comorbidity patterns were compared against the current classification of PH defined by the WHO.

**Results:** Network analysis of comorbidity data identified PH subtypes with known etiological basis, as defined by the WHO (Figure), thus lending credibility to the approach. The analysis further captured several under-recognized subtypes previously documented in a limited number of case reports, as well as comorbidity clusters that had not been previously reported, including rare genetic disorders such as Smith-Lemli-Opitz syndrome, type II glycogen storage disorder, and cri-du-chat syndrome.

**Conclusions:** We demonstrated the feasibility of applying network science to identify comorbidity-based subtypes that are biologically and clinically informative. The proposed approach facilitates identification of rare and novel subtypes. Further studies are needed to validate the clinical significance of the discovered subtypes.

Figure. Bayesian comorbidity network of children with pulmonary hypertension



Each node represents a comorbidity, and edges between nodes represent probabilistic dependencies between comorbidities.

#### 48. Improvements in Spina Bifida Associated Infant Mortality

Nelson D. Pace, David J. Wilde

Department of Epidemiology, University of North Carolina at Chapel Hill (NDP)  
School of Medicine, University of Texas Health Sciences Center at San Antonio (DJW)

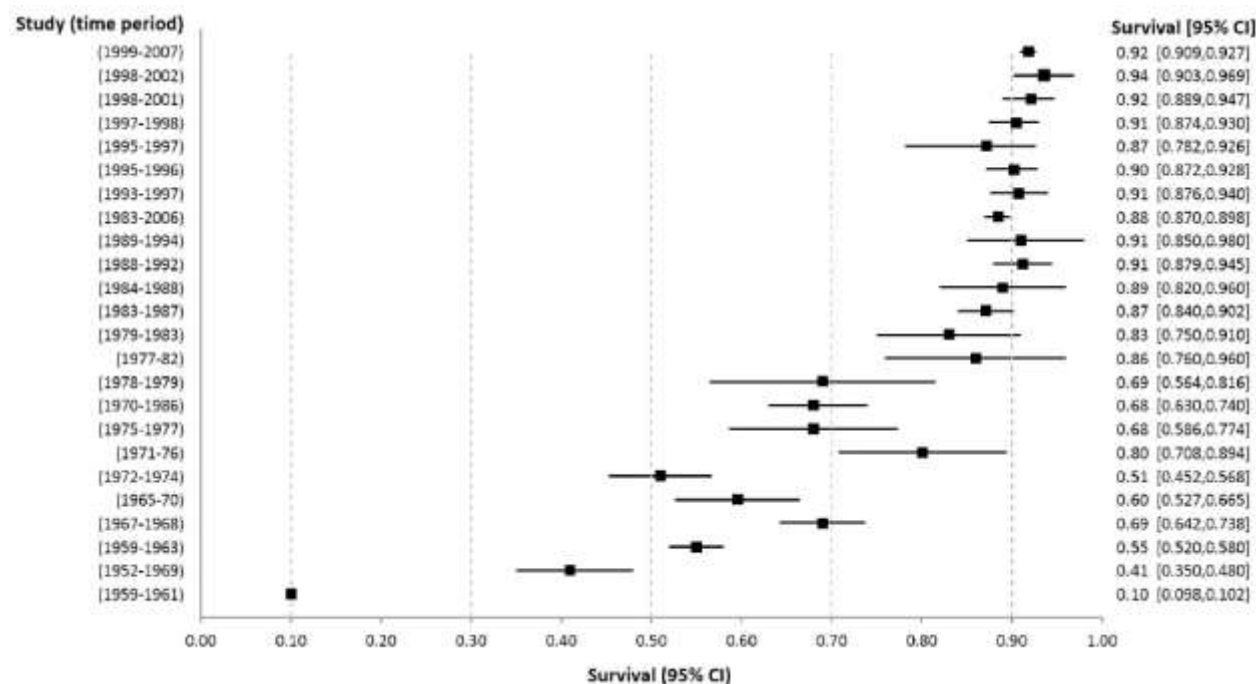
**Objective:** Over the past century, infant mortality, death of a liveborn child in the first year of life, has decreased in the US from 10 to 0.6%, a 94% reduction in infant mortality. Great efforts to prevent and treat disease have made this possible. Among the monumental advances in perinatal clinical care in last 50 years, has been the increased survival of infants born with a birth defect. Advancements in treatment and clinical decision-making have made some birth defects, like spina bifida, a congenital anomaly that rarely results in death. Spina bifida occurs in 1 out of every 3000 live born infants in the US.

**Methods:** We reviewed studies on survival among infants with spina bifida and present synthesized results of infant survival juxtaposed to advancements in clinical care.

**Results:** Whether or not to even treat an infant with spina bifida or when to treat was debated for several decades. Prior to the 1960s, only 11-30% of untreated infants with spina bifida survived beyond 6 months while 24-41% of treated cases survived beyond 1 year. Use of shunts to treat and prevent hydrocephalus paralleled survival rising to 60%. Improved shunts and antibiotic use (1970s) led to 60-86% survival. Survival of spina bifida has gradually improved to be currently between 92-97% due to antenatal detection and monitoring and improvements in surgery and post-operative care (1980s). Shunts and clinical guidelines to preform treatment soon after birth have likely resulted in the largest improvement in survival.

**Conclusions:** Spina bifida is a model for how other birth defects can improve survival through technological advancement and clinical guidelines.

Figure 1. One year survival estimates for infants born with spina bifida from original research articles





#### 49. Neuropsychological profile in Sjögren's syndrome.

Pérez Martínez, Sara.

Complutense University of Madrid (Spain). Department of Basic Psychology.

Quaes Foundation (Valencia, Spain)

**Objective.** Sjögren's syndrome (SS), ORPHA 378, is a chronic autoimmune disorder of unknown etiology. Considered rare disease that affects people of all ages, being more prevalent in women between 40 and 50 years (female to male ratio of 9: 1). The study of this disease has made us advance the development of new diagnostic and therapeutic approaches, including neuropsychological (cognitive, emotional and functional profile) and its relationship to the quality of life of those affected. The aim of our study is to investigate and describe the neuropsychological profile of a sample of people with Sjögren's syndrome.

**Methods.** All published papers on the topic of neuropsychological deficits in SS on Medline and other databases were reviewed. We report updated findings from descriptive analyses of neuropsychological data from 11 Spanish-speaking women with the Sjögren Syndrome. We use a standard neuropsychological test battery.

**Results.** Our sample with SS had significantly low performance in attention and inhibition domain tested, processing speed and executive function.

**Conclusions.** Patients with Sjögren Syndrome had cognitive deficits in multiple areas. Our results support the existing literature. We consider it appropriate to propose the study of the central nervous system including neuropsychological assessment as a means of improving our interventions and quality of life of patients.

#### 50. Cortical excitability is not different between healthy controls and people with laryngeal dystonia

Cecília N. Prudente<sup>1</sup>, Mo Chen<sup>1</sup>, Rebekah L. Schmidt<sup>1</sup>, George S. Goding<sup>2</sup>,

Sharyl Samargia<sup>3</sup>, Christy L. Ludlow<sup>4</sup>, Teresa J. Kimberley<sup>1</sup>

1. Department of Rehabilitation Medicine, University of Minnesota

2. Department of Otolaryngology, Head and Neck Surgery, University of Minnesota

3. Department of Communication Sciences and Disorders, University of Wisconsin River Falls

4. Department of Communication Sciences and Disorders, James Madison University

**Objective:** Adductor spasmodic dysphonia (AdSD), the primary form of laryngeal dystonia, is characterized by involuntary contractions of the thyroarytenoid muscle. Studies using transcranial magnetic stimulation (TMS) have reported decreased intracortical inhibition in unaffected muscles in AdSD, such as a hand muscle and the masseter. However, it is unknown if there is altered cortical excitability in the laryngeal motor cortex in AdSD. The purpose of this study was to compare the cortical excitability of the laryngeal motor cortex between healthy controls and people with AdSD.

**Methods:** In 11 healthy controls and 14 people with AdSD, fine-wire electrodes were used to record bilateral responses of the thyroarytenoid to single pulse TMS stimuli. TMS pulses were delivered to the laryngeal motor cortex in both hemispheres. The duration of the cortical silent period (CSP) was used as a measure of cortical excitability. CSP is defined as a period of interruption of voluntary muscle activity during TMS pulse delivery and it is thought to reflect spinal and cortical inhibitory mechanisms. The latencies of responses to cortical stimulation were also measured in both groups. Responses to peripheral stimulation delivered to the vagus nerve branch at level of the mastoid were collected for comparison.

**Results:** Average  $\pm$  SD duration of CSP was  $49.9 \pm 17.9$ ms in controls and  $47.0 \pm 14.6$ ms in participants with AdSD. Cortical latency of responses was  $13.2 \pm 5.2$  and  $14.0 \pm 4.5$ ms in controls and AdSD, respectively. Peripheral latency responses were  $7.0 \pm 2.8$ ms in controls and  $6.0 \pm 3.1$ ms in AdSD. Between-groups comparisons for CSP duration revealed no significant differences. In addition, cortical and peripheral latencies were not significantly different between groups.

**Conclusions:** The findings suggest that excitability of the laryngeal motor cortex measured is not different between healthy controls and people with AdSD. Reasons for the lack of decreased inhibition in AdSD are unclear. Factors that need to be considered are the methods used (fine-wire vs. surface electrodes in previous studies), the unique neural control of laryngeal muscles, and the pathogenesis of AdSD.

## 51. Helping Patients to Navigate the Clinical-Research Divide

Kimberly Splinter<sup>1</sup>, Matthew Might<sup>1,2</sup>, Cecilia Esteves<sup>1</sup>, Isaac Kohane<sup>1</sup>, Rachel Ramoni<sup>1,3</sup>

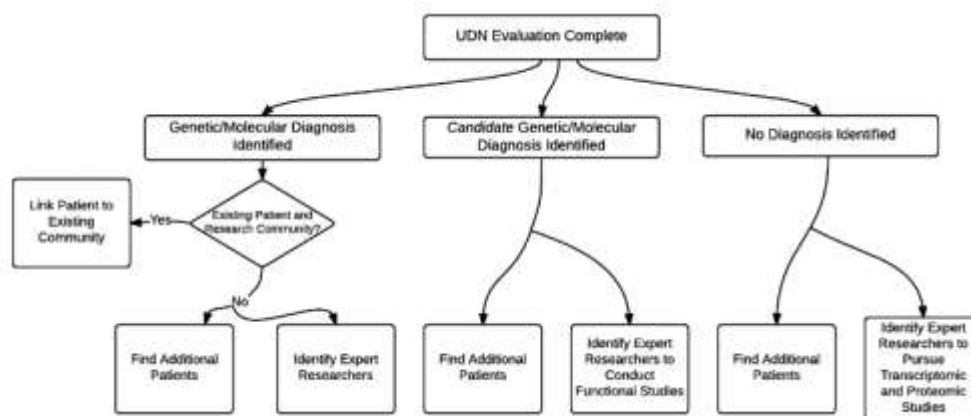
<sup>1</sup>Department of Biomedical Informatics, Harvard Medical School

<sup>2</sup>School of Computing, University of Utah

<sup>3</sup>Department of Epidemiology and Health Promotion, New York University College of Dentistry

**Objective:** While receiving a diagnosis marks the end of one journey for participants in the Undiagnosed Diseases Network (UDN) (Grant Number: U01HG007530), it often signals the beginning of a research phase to understand and treat the condition. Previously UDN participants were matched to basic researchers through either a protracted grant process or serendipitously identifying researchers known to investigators at one of the seven UDN clinical sites. Following this approach, not all participants are matched with researchers and results are not gathered consistently, which may delay the identification of significant findings. To bring the benefits of basic research to more participants and improve the efficiency of this process, we are piloting a new role in the UDN: Participant Research Navigator (PRN).

**Methods:** UDN participants with completed clinical evaluations were categorized as having a genetic/molecular diagnosis, a candidate genetic/molecular diagnosis, or no diagnosis. For each participant, the PRN process, outlined in the figure below, was piloted. Expert researchers were identified using Profiles Research Network Software and Google searches. These expert researchers were reviewed with the UDN clinical sites. To find additional patients with the same or similar condition, available participant data was shared in PhenomeCentral and on UDN webpages. The operational aspects of this process were led by a genetic counselor (K.S.).



**Results:** As of September 30, 2016, 90 participant records had been reviewed for potential basic research matches. 11 expert researcher suggestions were made through the PRN process; 3 of these suggestions will be pursued by the participant's clinical site. Research follow-up for all participants will be tracked. Additionally, 11 potential and 2 actual patient matches were identified through the participant webpages and 4 potential patient matches were identified through PhenomeCentral.

**Conclusions:** For individuals whose conditions are not yet understood by medicine, basic science is a necessary next step. Here we describe a novel role and process for the transition to basic research in the UDN, which if successful, could be implemented beyond the UDN.

## 52. Development of a Pregnancy Self-Report Survey for Osteogenesis Imperfecta

Rashmi Rao MD<sup>1</sup>, Deborah Krakow MD<sup>2</sup>. <sup>1</sup> University of California, Los Angeles Department of Obstetrics and Gynecology.  
<sup>2</sup> University of California, Los Angeles Department of Orthopaedic Surgery

**Objective:** Pregnancy causes numerous physiologic changes and adaptations that can exacerbate already stressed organ systems, particularly the skeleton. Data on pregnancy, maternal and fetal outcomes, and lactation in women with the rare disease, osteogenesis imperfecta (OI), is very limited. The purpose of this study is to develop a pregnancy survey in order to characterize the course and outcomes of pregnancies in individuals affected by OI. The knowledge gained from this study will be instrumental in developing objective data on pregnancy outcomes in women with OI.

**Methods:** The Rare Disease Clinical Research Network Brittle Bone Disorders (RDCRN BBN) Contact Registry helps researchers identify and recruit patients who are eligible for participation in future research studies. The inclusion criteria for our study includes: women with OI who are registered in the BBD Contact Registry. In addition, the women must have been pregnant with subsequent delivery of a neonate after 24 weeks gestation. Exclusion criteria include: inability to provide informed consent, males, and women with OI who have not delivered children, and gestations associated with higher order multiples. We developed a self-report survey in order to assess pregnancy characteristics and outcomes (maternal and fetal) of those affected by OI. The survey includes questions constructed to ascertain information such as: medication use, exercise ability, pregnancy complications, delivery and neonatal characteristics. Measures of pregnancy outcome include: length of gestation, mode of delivery, neonatal outcomes, history of fractures during pregnancy or postpartum, number of hospital admissions, calcium and vitamin D intake, neonatal complications, and OI status in the fetus.

**Results and Conclusion:** The pregnancy self report survey for OI has been IRB approved through the University of California, Los Angeles. Final approval is pending through the Brittle Bone Disorders Consortium. Once final approval is obtained, patients will be sent an email invitation describing the study. Patients that are willing to participate will be directed to an IRB-approved online consent form. The survey data will be collected and stored at the RDCN Data Management and Coordinating Center. Upon conclusion of the study period, the data will be sent to the Osteogenesis Imperfecta Foundation. All data collected will be sent to the database of Genotypes and Phenotypes to be stored indefinitely.

## 53. Validation of a Diary Score for Assessment of Symptom Pattern and Treatment Response in Sting-Associated Vasculopathy with Onset in Infancy (SAVI) and Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature (CANDLE)

Megha Sawhney<sup>1</sup>, Gina Montealegre<sup>2</sup>, Robert Wesley<sup>3</sup>, Kost Bahar<sup>1</sup>, Raphaela Goldbach-Mansky<sup>2</sup>

<sup>1</sup>Rheumatology Fellowship Program, National Institutes of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

<sup>2</sup>Translational Autoinflammatory Disease Studies, National Institute of Allergy and Infectious Diseases (NIAID)

<sup>3</sup>Clinical Center, NIH

**Objective:** CANDLE and SAVI are two rare autoinflammatory interferonopathies without validated outcome measures to assess disease activity. Daily diaries have become standard in assessing clinical disease load and reporting treatment related outcomes in CAPS (Cryopyrin associated periodic syndrome). Our study validates diary score as an instrument to assess symptom pattern and response to treatment in CANDLE and SAVI patients.

**Methods:** The daily diary developed for NOMID was modified to reflect disease symptoms of CANDLE and SAVI. For CANDLE these include: fever, rash, joint pain, headache and fatigue (possible range, 0 to 20) For SAVI these also include respiratory symptoms and ulcerative lesions. Each symptom is rated on a scale from 0 to 4 for increasing severity. We correlated the diary score in CANDLE and SAVI patients against 6 validated outcome measures: Childhood Health Assessment Questionnaire (CHAQ), which measures physical function; physical global VAS (PHYG); global pain assessment (PAINGL); parent global (PARG); the patient quality of life (PATQL) and parent QL (PARQL) by correlating each symptom and the summary score with PHYG, PAINGL, PARG, PATQL and PARQL respectively. We used Pearson correlation and 1-sample t- test to assess whether these values plausibly centered at 0. P – values were not corrected for multiple comparisons but p-values of <0.01 were considered significant.

**Results:** 11 CANDLE and 4 SAVI patients and 3 undifferentiated interferonopathy patients were included. Mean diary scores computed for all patients correlated well with CHAQ (r-0.36, p<0.001). Mean diary score computed during the evaluation for CANDLE patients correlated well with CHAQ (r-0.36, p<0.001), pain global (r- 0.48, p<0.001). Individual symptoms like fever, rash etc correlated well with these outcome measures in both CANDLE and SAVI. However, the SAVI specific parameters, respiratory symptoms and ulcerative lesions did not show any significant correlation.

**Conclusion:** Our study shows that diary scores exhibit validity across other outcome measures validated for unrelated pediatric inflammatory diseases, but outcome measures in SAVI need to be further refined.

### 54. Scarless gene correction of arginase-1 deficiency in mouse iPSCs using CRISPR/Cas9-mediated gene targeting and *piggyBac* transposase

Yuan Yan Sin, Phillippe Price, Laurel Ballantyne, Crystal McCracken, Colin D. Funk

Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON K7L 3N6 Canada

**Objective:** Arginase-1 deficiency is an inborn error of metabolism resulting from a loss of the liver-type arginase-1 (Arg-1), leading to impaired ureagenesis. We previously generated a tamoxifen-induced Arg-1 deficient mouse model harboring a deletion of *Arg1* exons 7 and 8 that leads to hyperargininemia and other metabolic derangements. Here, we applied Clustered Regularly Interspaced Short Palindromic Repeats (CRISPRs)/CRISPR-associated protein (Cas9) system in combination with *piggyBac* technology to target and reincorporate exons 7 and 8 at the specific locus to restore normal function of Arg-1.

**Methods:** Mouse embryonic fibroblasts (MEFs) obtained from the inducible Arg-1 deficient mice were treated with tamoxifen *in vitro* to induce the deletion of *Arg1* exons 7 and 8, and reprogrammed into induced pluripotent stem cells (iPSCs) as a model to exploit our gene-editing strategy. We utilized CRISPR/Cas9 system to mediate genetic alteration in intron 6 of the *Arg1* locus for the reincorporation of exons 7 and 8. After sequence validation, the repaired mouse iPSCs were differentiated into hepatocyte-like cells to verify functional corrections.

**Results:** Arg-1 deficient MEFs were reprogrammed into iPSCs using a lentiviral reprogramming method and were characterized for pluripotency via alkaline phosphatase staining, immunocytochemistry and *in vivo* teratoma formation. Genetic correction of *Arg-1* was achieved *in vitro* through CRISPR/Cas9-mediated homology-directed repair (HDR) using a donor template containing wild-type exons 7 and 8 cDNA. Two rounds of genetic manipulation which consist of *piggyBac* transposase with drug selection-based enrichment of genetic modifications were carried out. Our results show that CRISPR/Cas9 efficiently cleaves chromosomal DNA at the precise location (indel frequency  $\approx 12\%$ ). PCR-based screening and sequencing results confirmed correct incorporation of exons 7 and 8 at the specific *Arg1* locus. The transgene-free repaired cells were expanded for differentiation into hepatocyte-like cells to verify functional corrections. Transplantation of repaired hepatocyte-like cells into our knockout mice is being carried out to demonstrate potential *in vivo* recovery of Arg-1 deficiency and provide insights into disease mechanism.

**Conclusions:** Our study provides proof-of-concept for precision gene-editing utilizing CRISPR/Cas9-mediated HDR in Arg1-deficient mouse-derived cells. Successful restoration of Arg-1 function could facilitate the development of autologous cell replacement therapies for urea cycle disorders and potentially other disorders that are refractory to traditional therapies.

### 55. Specific targeting of E3s augments CFTR correction and function.

Riling, Christopher<sup>1</sup>; Sterner, David<sup>1</sup>; Wu, Jian<sup>1</sup>; Sokirniy, Ivan<sup>1</sup>; Chung, Wook Joon<sup>2,3</sup>; Fortenberry, James<sup>2</sup>; Zhang, Zairong<sup>1</sup>; Butt, Tauseef<sup>1</sup>; Chiang, Annette<sup>4</sup>; Goeckeler-Fried, Jennifer<sup>4</sup>; Brodsky, Jeffrey<sup>4</sup>; Sorscher, Eric J.<sup>2,5</sup>; Mattern, Michael<sup>1</sup>; Kumar, Suresh<sup>1</sup>

1. Progenra Inc, Malvern, PA, USA.

2. Cystic Fibrosis Research Center, Univ of Alabama at Birmingham, Birmingham, AL, USA

3. Neurobiology, Univ of Alabama at Birmingham, Birmingham, AL, USA

4. Biological Sciences, Univ of Pittsburgh, Pittsburgh, PA, USA

5. Medicine, Univ of Alabama at Birmingham, Birmingham, AL, USA

**Objective:** To discover and develop gp78 and CHIP inhibitors as 'protectors' for rescuing  $\Delta F508$ -CFTR from degradation and promoting transport to the PM in combination with correctors.

**Methods:** Using the UbiPro<sup>TM</sup> discovery platform Progenra conducted HTS and discovered gp78 and CHIP inhibitors. These inhibitors were evaluated for their ability to increase levels of  $\Delta F508$ -CFTR and rescue by lumacaftor. CFTR channel assays were utilized to monitor the efficacy of compounds.

**Results:** We found that expression of  $\Delta F508$ -CFTR can be markedly increased by interrupting ER-associated degradation (ERAD), and that blocking activity of the ubiquitin cascade increases CFTR and synergistically augments  $\Delta F508$ -CFTR correction when used in combination with lumacaftor. Several compounds were seen to 1) stabilize  $\Delta F508$ -CFTR Band B, 2) augment  $\Delta F508$ -CFTR Band C levels in combination with lumacaftor, and 3) enhance  $\Delta F508$ -CFTR ion transport in human bronchial epithelial monolayers synergistically with lumacaftor.

**Conclusions:** These results support blockade of specific ubiquitin ligases as a valuable drug development strategy to promote "repairable"  $\Delta F508$ -CFTR. Considering the diversity of ubiquitin ligases, compounds that selectively target E3s may provide clinically relevant levels of  $\Delta F508$ -CFTR for compound heterozygotes or other patients with class II mutations. Lead optimization and ADME/PK evaluation are currently in progress. Development of these compounds may provide transformative therapeutic agents for cystic fibrosis.

## 56. Endocytic alterations in Lysosomal Storage Diseases human brains

Melani A. Solomon<sup>1</sup>, Ronaldo Moscoso<sup>1</sup>, Ronelle Bautista<sup>2</sup>, Silvia Muro<sup>1,2</sup>

<sup>1</sup>Institute of Bioscience and Biotechnology Research, University of Maryland, College Park, USA

<sup>2</sup>Fischell Department of Bioengineering, University of Maryland, College Park, USA

**Objective:** Lysosomal storage diseases (LSDs) are a group of 50 distinct inherited disorders caused due to the deficiency of lysosomal hydrolases which cause accumulation of non-degraded substrates in cells. Build-up of materials in cells have been shown to impede normal endocytosis processes in several disease models, including LSDs. Since neurodegeneration is observed with most LSDs, it is important to examine the endocytic disturbances in brains of such patients since they can also limit the uptake of therapeutics into the brain. This work assessed the status of clathrin-mediated (CME), caveolae-mediated (CavME) and cell-adhesion molecule mediated (CAM) endocytosis pathways in brains of LSD patients.

**Methods:** Post-mortem human brains from 7 early-onset and 3 late-onset LSDs were evaluated for the expression of the following markers: dynamin (necessary for all forms of endocytosis), clathrin heavy chain (CHC, associated to CME), caveolin-1 (associated to CavME) and Intercellular Cell Adhesion Molecule (ICAM-1, associated to CAM). These were determined by western blotting and immunohistochemistry on brain samples wherein 3-4 replicates of each assay were conducted. Statistical significance was determined by ANOVA.

**Results:** In the early-onset LSD brains studied, expression of dynamin, CHC and caveolin-1 decreased to 3%, 24% and 20% respectively as compared to age-matched control brains. In the late-onset forms, dynamin and CHC decreased to 22% and 25% respectively while caveolin-1 expression remained unchanged. These alterations were observed in all LSD subtypes- leukodystrophies, sphingolipidoses and lipidoses suggesting that endocytic dysfunction, even in brains, is a secondary effect of storage in LSDs. However, ICAM-1 expression was 1.5 to 3-fold higher in early- and late-onset brains compared to controls, possibly as a compensatory mechanism or as a consequence of inflammation seen in LSDs.

**Conclusions:** These results indicate that the endocytic machinery in brains of patients with LSDs is affected, the more severe (early-onset) forms of the disease exhibiting greater perturbations. From the therapeutic stand-point, such alterations must be considered while designing drug delivery systems for treating neurodegenerative diseases that exhibit abnormal cell storage. Based on this work, the ICAM-1 receptor expression was increased in all the LSD brain samples tested suggesting that this pathway is less affected in LSDs and could be targeted for therapeutic delivery in LSDs.

## 57. Volumetric Analysis of the Basal Ganglia in Patients with Phelan-McDermid Syndrome

Siddharth Srivastava<sup>1</sup>, Anna Prohl<sup>2</sup>, Benoit Scherrer<sup>2</sup>, Simon K. Warfield<sup>2</sup>, Mustafa Sahin<sup>1</sup>

<sup>1</sup>Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA

<sup>2</sup>Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA

**Objective:** Phelan-McDermid Syndrome (PMS) is a disorder of synaptic transmission caused by a defect in *SHANK3*, either through an intragenic mutation or a 22q13 deletion encompassing the gene. Affected patients present with a variety of somatic and neurobehavioral features, including minor systemic anomalies, normal to advanced growth, intellectual disability, autism spectrum disorder, and generalized hypotonia. Knowledge about altered neuroanatomical circuitry in PMS comes from mice models showing evidence of abnormally shaped striatal neurons and striatal hypertrophy in the basal ganglia. To date, very few studies have evaluated evidence of striatal hypertrophy in humans with PMS.

**Methods:** We performed volumetric analysis on baseline brain MRIs of patients (ages 3-21 years) with PMS enrolled in a prospective observational cohort study evaluating the genotype, phenotype, and natural history of PMS (ClinicalTrials NCT02461420). Using segmentations of the MRI carried out with the previously described and validated PSTAPLE algorithm (<https://www.ncbi.nlm.nih.gov/pubmed/23744673>), we measured the volumes of 4 anatomical structures (averaged between left and right): caudate, putamen, globus pallidus, and thalamus. We compared these measurements to those of age- and sex-matched healthy controls who were part of a separate study.

**Results:** Eight patients with PMS (4 females, 4 males) and 8 healthy controls (4 females, 4 males) were part of this analysis. At time of brain MRI, the mean age of the patients and controls was  $8.86 \pm 3.88$  years (range 3.43-15.09 years) and  $8.99 \pm 4.02$  years (range 3.12-15.34 years), respectively ( $p = 0.95$ ). Putamen volume was slightly decreased in patients ( $4796.19 \pm 639.24 \text{ mm}^3$ ) compared to controls ( $5415.37 \pm 503.65 \text{ mm}^3$ ) ( $p = 0.049$ ). There was no significant difference in volumes of the caudate ( $p = 0.82$ ), globus pallidus ( $p = 0.43$ ), or thalamus ( $p = 0.98$ ).

**Conclusions:** The volume of the putamen, but not other parts of the basal ganglia or thalamus, is decreased in children with PMS based on volumetric analysis of MRI data. This finding is contrary to the animal model data, but warrants further investigation with larger numbers of patients.

# 58. Double Support Times During Treadmill Walking Are Associated With *MECP2* Mutation Type In Rett Syndrome

Bernhard Suter<sup>1</sup>, David Young<sup>2,3</sup>, Beom-Chan Lee<sup>2,3</sup>, Daniel G. Glaze<sup>1</sup>, Charles S. Layne<sup>2,3</sup>

<sup>1</sup>Blue Bird Circle Rett Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, <sup>2</sup>Center for Neuromotor and Biomechanics Research, <sup>3</sup>Department of Health and Human Performance, University of Houston, Houston, TX

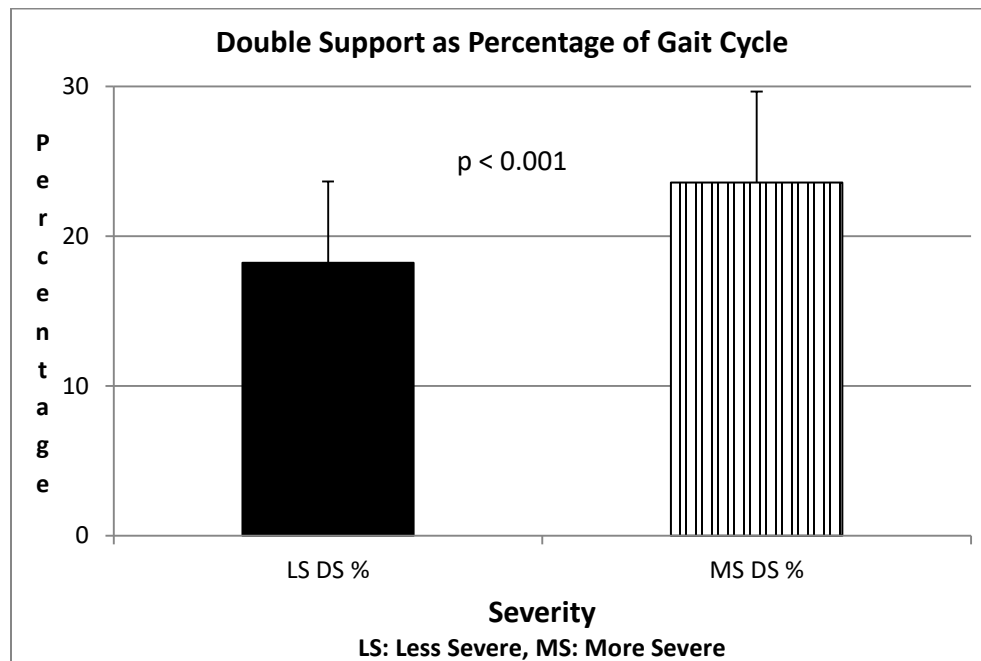
**Objective:** To determine if *MECP2* mutation type in Rett Syndrome is associated with temporal gait parameters during treadmill walking.

**Methods:** Twenty Rett patients ( $\bar{X}$  = 10.9 age, SD = 6.5) walked on a motorized treadmill as belt speed was increased in 0.1 m/s increments. This protocol enabled us to determine how participants adapted their gait parameters to treadmill speed increases. Absolute stride times, stance times, and double support times for both limbs were obtained for each treadmill speed. These measures were also calculated as a percentage of the gait cycle. The participants were separated into two groups (Less Severe and More Severe) based upon their *MECP2* mutation, which has been reported to affect the severity of their condition (Cuddapah et al., 2014). The measures tested to determine if mutation type predicted differences between the two groups.

**Results:** Both groups were effectively able to adapt to the changing treadmill speeds. The More Severe group displayed a significant increase in double support time relative to the Less Severe group, independent of treadmill speed.

**Conclusions:** Consistent with the Cuddapah et al., (2014) report that *MECP2* mutation is related to symptom severity, our data indicate those participants categorized as Most Severe displayed increased double support times. Increases in double support time are associated with strategies intended to increase balance control during gait suggesting our Most Severe participants faced increased postural control challenges while walking.

*Supported by Blue Bird Circle Rett Center*



### 59. Surgical Outcomes for Brain Arteriovenous Malformation Resection in Patients with Hereditary Hemorrhagic Telangiectasia

Ali Tayebi Meybodi, MD<sup>1</sup>, Helen Kim, PhD<sup>2,4</sup>, Jeffrey Nelson, MS<sup>2,4</sup>, Steven W. Hetts, MD<sup>3,4</sup>, Timo Krings, MD<sup>5</sup>, Karel G. terBrugge<sup>5</sup>, Marie E. Faughnan, MD, MSc<sup>6</sup>, Michael T. Lawton, MD<sup>1,2,4</sup>, and the Brain Vascular Malformations Consortium HHT Investigator Group<sup>‡</sup>,

<sup>1</sup>Department of Neurological Surgery, University of California, San Francisco, <sup>2</sup>Department of Anesthesia and Perioperative Care, University of California, San Francisco, <sup>3</sup>Division of Neurointerventional Radiology, Department of Radiology and Biomedical Imaging, University of California, San Francisco, <sup>4</sup>Center for Cerebrovascular Research, University of California, San Francisco, <sup>5</sup>Division of Neuroradiology, Department of Medical Imaging, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada,

<sup>6</sup>Division of Respiriology, Keenan Research centre, and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

<sup>‡</sup> Brain Vascular Malformation Consortium HHT Investigator Group: Murali Chakinala, Marianne Clancy, Marie E. Faughnan, James R. Gossage, Katharine Henderson, Steven Hetts, Vivek Iyer, Raj Kasthuri, Helen Kim, Timo Krings, Michael T. Lawton, Doris Lin, Johannes Jurgen Mager, Charles E. McCulloch, Justin McWilliams, Jamie McDonald, Ludmila Pawlikowska, Jeffrey Pollak, Felix Ratjen, Karen Swanson, Karel terBrugge, Dilini Vethanayagam, Andrew White, Robert I. White Jr, Pearce Wilcox

**Objective:** Cerebral arteriovenous malformations (AVM) are common in patients with hereditary hemorrhagic telangiectasia (HHT). However, due to rarity of HHT, there is little published evidence of outcomes from management of brain AVMs in this disease. Current International HHT Guidelines recommend an individualized approach by a multidisciplinary team with neurovascular expertise. Specifically, the outcomes for surgical resection of these lesions have not been reported to date. We report outcomes of surgical resection of brain AVMs in HHT patients.

**Methods:** From the Brain Vascular Malformation Consortium HHT project database, 19 patients with 20 resected AVMs were studied. Patients were retrospectively reviewed for pre-operative, early, and late post-operative functional status (modified Rankin Scale [mRS] score).

**Results:** The median pre-operative, early post-operative and late post-operative mRS scores of the patients were 1. At late follow up, 74% of the patients were in good functional status (mRS scores 0 and 1).

**Conclusion:** HHT patients treated surgically for brain AVMs appear to have good long-term functional outcomes. It is therefore reasonable to continue to consider surgical resection as an option in the multidisciplinary team's individualized treatment strategy for HHT patients with brain AVMs.



# 60. Longitudinal Trends in Respiratory Microbiology and Pulmonary Function in Primary Ciliary Dyskinesia: Comparisons to a Cystic Fibrosis Cohort

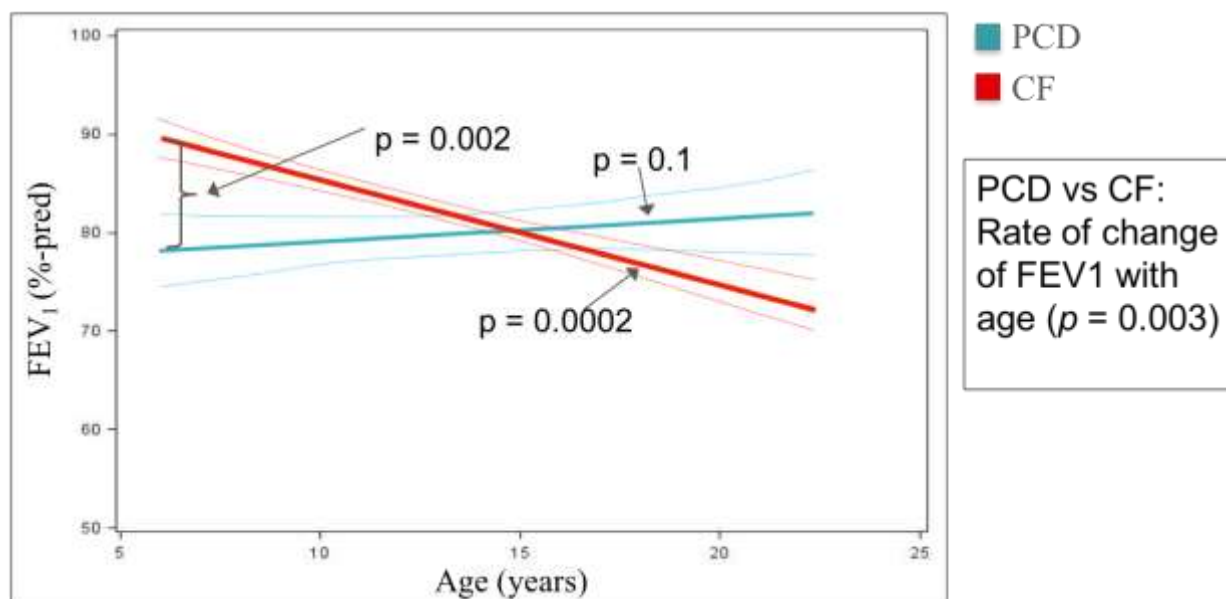
M.C. Tracy, J.M. Zirbes, C. Hernandez, C.E. Milla;  
Stanford University School of Medicine, Palo Alto, CA/US

**Objectives:** Primary ciliary dyskinesia (PCD) is a rare disease, characterized by chronic oto-sino-pulmonary infections. Respiratory microbiology in PCD is presumed similar to that seen in cystic fibrosis (CF) in its composition and associated morbidity. We hypothesized that in patients with PCD respiratory microbiology and its longitudinal association with pulmonary function diverges from that of CF patients.

**Methods:** A retrospective review of respiratory culture results and pulmonary function data of pediatric PCD and CF patients at our center from 2011-2016 was performed.

**Results:** There were 37 PCD patients, and 189 CF patients (mean age 11.8 years PCD, 10.7 years CF.) PCD patients had a higher frequency of negative cultures, compared to CF patients (62% PCD, 42% CF,  $p = 0.001$ ), and a higher frequency of *H. influenza* (19% PCD, 10% in CF,  $p = 0.01$ ). In contrast, the frequency of *S. aureus* in CF was greater than PCD (29% PCD, 50% CF,  $p = 0.001$ ), as was the frequency of *P. aeruginosa* (16% PCD, 23% CF,  $p = 0.01$ ).

Longitudinal analysis of pulmonary function by FEV<sub>1</sub> %-pred. (Figure) revealed important differences. CF patients experienced a significant decline ( $p=0.0002$ ), whereas PCD patients appeared stable with a trend for improvement ( $p=0.1$ ). An effect for respiratory microbiology on FEV<sub>1</sub> was detected for both groups, though an association with *P. aeruginosa* was only observed in CF ( $p = 0.002$ ).



**Conclusions:** Respiratory microbiology differs substantially between children with PCD and CF. Pulmonary function in this pediatric cohort appears more stable in PCD compared to CF, with a differential impact of associated microbiology. These findings have important clinical and infection control implications.



## 61. Atypical Femur Fractures in Osteogenesis Imperfecta

Pamela Trejo, Francis H. Glorieux and Frank Rauch.  
Shriners Hospital for Children Canada and McGill University

**Introduction:** Recent case reports have described atypical femur fractures (AFF; fractures affecting subtrochanteric and diaphyseal areas of the femur) as a complication of long-term bisphosphonate treatment in children with osteogenesis imperfecta (OI). However, it is not clear whether AFF in children with OI are actually associated with bisphosphonate treatment or rather are related to the disease.

**Objective:** Assess the characteristics of subtrochanteric and diaphyseal femur fractures in children with osteogenesis imperfecta (OI) with and without BP treatment to investigate if there is a relationship between BP treatment and atypical femur fractures (AFF).

**Methods:** We did a retrospective chart review to assess the characteristics of subtrochanteric and diaphyseal fractures of non-deformed femurs in children with OI who had not undergone intramedullary rodding procedures.

**Results:** We identified 195 femur fractures (in 132 patients) for which radiographic documentation at the time of the fracture was available. After exclusion of fractures that occurred in deformed femurs or after intramedullary rodding surgery, 36 fractures (in 33 children) were evaluated for AFF criteria. Of these, 9 fractures (in 8 children; median age at fracture 3.7 years, range 3 months to 17.4 years; 5 boys) occurred during bisphosphonate treatment. Three of these fractures (in 3 children; median age at fracture 6.2 years; range 3.7 to 7.1 years; 2 boys) fulfilled the criteria for AFF. Among the 27 femur fractures that occurred in the absence of prior bisphosphonate treatment (25 patients; median age at fracture of 2.3 years, range 1 month to 13.4 years; 10 boys), 14 fulfilled the AFF criteria (13 patients; median age at fracture 2.8 years, range 1.5 to 13.4 years; 5 boys). Thus, AFF were found in 3 of 9 (33%) femur fractures that occurred during bisphosphonate treatment and in 14 of 27 (52%) femur fractures that occurred in the absence of bisphosphonate treatment. Logistic regression analysis found that AFF were associated with the severity of OI but not with bisphosphonate treatment.

**Conclusion:** The present study suggests that AFF in children with OI are part of the disease process rather than an adverse event of bisphosphonate therapy.

## 62. In-depth characterization of patients with repeat expansions in *C9ORF72*

Marka van Blitterswijk,<sup>1</sup> NiCole A. Finch,<sup>1</sup> Mariely DeJesus-Hernandez,<sup>1</sup> Tania F. Gendron,<sup>1</sup> Keith A. Josephs,

<sup>2</sup> Joseph E. Parisi,<sup>2</sup> David S. Knopman,<sup>2</sup> Ronald C. Petersen,<sup>2</sup> Bradley F. Boeve,<sup>2</sup> Neill R. Graff-Radford,

<sup>3</sup> Leonard Petrucelli,<sup>1</sup> Dennis W. Dickson,<sup>1</sup> Kevin B. Boylan,<sup>3</sup> and Rosa Rademakers<sup>1</sup>

<sup>1</sup>Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA, <sup>2</sup>Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA, and <sup>3</sup>Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

**Objective:** Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder; its most common genetic cause is a repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*). Importantly, this repeat expansion is also a frequent cause of frontotemporal dementia (FTD), and is occasionally detected in patients with other diseases, such as Alzheimer's disease (AD). We already evaluated *C9ORF72* expression levels, the length of the repeat expansion, and dipeptide-repeat proteins aberrantly translated from the repeat. In our present study, we assessed methylation levels of the *C9ORF72* promoter and quantified the number of RNA foci that contain flawed RNA transcripts, in an ongoing effort to elucidate the clinical variability and the mechanism underlying *C9ORF72*-related diseases.

**Methods:** We examined a cohort of more than fifty *C9ORF72* expansion carriers for whom blood, cerebellum, and/or frontal cortex were available; all patients were obtained at Mayo Clinic. We performed methylation-sensitive restriction enzyme digests to examine methylation levels, and additionally, we used RNA fluorescent in situ hybridization (FISH) to quantify the number of RNA foci.

**Results:** Our methylation analysis revealed hypermethylation of the *C9ORF72* promoter in 27% of blood samples, whereas hypermethylation was only detected in 9% of samples obtained from the cerebellum or frontal cortex. In the cerebellum, 22% of cells contained RNA foci and the average number of RNA foci was 1.4 in those cells. In the frontal cortex, 30% of cells harbored RNA foci with, on average, 2.3 RNA foci per cell. Remarkably, in the cerebellum, the individual with the highest percentage of RNA foci was a female patient with a pathological diagnosis of AD: RNA foci were present in 54% of cells.

**Conclusions:** Much remains unknown about the underpinnings of diseases linked to a repeat expansion in *C9ORF72*. Our thorough characterization of patients harboring this expansion, however, helps to increase our understanding of these devastating diseases.

**63. A Prospective, Multicenter Study of Differential Clinical Characteristics of Adults and Children with Eosinophilic Gastrointestinal Diseases (OMEGA)**

Venter C<sup>1</sup>, Furuta GT<sup>1</sup>, Aceves SS<sup>1</sup>, , Carpenter C<sup>1</sup>, Dellon ES<sup>1</sup>, Falk GW<sup>1</sup>, Gonsalves NP<sup>1</sup>, Gupta SK<sup>1</sup>, Hirano I<sup>1</sup>, Kantor S<sup>1</sup>, Leung J<sup>1</sup>, Spergel JM<sup>1</sup>, Wershil BK<sup>1</sup>, Kuhl JT<sup>1</sup>, Rothenberg ME<sup>1</sup>

<sup>1</sup> Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)

**Objectives:** Eosinophilic gastrointestinal diseases (EGIDs) include eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), and eosinophilic colitis (EC). We analyzed clinical features, treatment (diet, steroids, diet/steroids), and anthropometrics of children and adults enrolled in the OMEGA longitudinal study of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR).

**Methods:** Recruitment started in January 2015. Data on diagnosis, age, treatment, and anthropometric measures was gathered, analyzed (descriptive statistics and Fisher's exact or Chi square) for significant differences, and tested for normality (Shapiro-Wilk test).

**Results:** Of the 202 participants recruited as of September 14, 2016, medical history was available for 101 (57 adults, 44 children). We found no statistical difference between adults and children for diagnosis of EoE (91.2% vs. 88.6%;  $p=0.74$ ), EG (5.3% vs. 13.6%;  $p=0.17$ ), or EC (5.3% vs. 4.5 %;  $p=1.00$ ) nor the use of diet (59.6% vs. 64.1%;  $p=0.83$ ), steroid (61.5% vs. 77%;  $p=0.17$ ), or dual (diet/steroid) (34.6% vs. 48.7%;  $p=0.20$ ) therapy. The use of proton-pump inhibitor (PPI) therapy for 8 weeks prior to the diagnostic esophagogastroduodenoscopy was significantly different (adults 94.2 % vs. children 61.5%;  $p<0.001$ ), but high-dose PPI (80.8% vs. 71.8%;  $p=0.33$ ) therapy use did not significantly differ. For EG and EC, treatment type varied by age group.

Body mass index (BMI) for adults and BMI percentiles for children with EoE were not normally distributed. For adults, 31% were overweight, 60% had a normal BMI, and 9% were underweight; BMIs ranged from 16–49 (median 23.5; IQR 6). For children, 14% were overweight, 79% were normal weight, and 7% were underweight. The BMI percentile range for boys was 2nd-99th (median 51.4th; IQR 33) and for girls was 0-95th (median 33.15th; IQR 77). BMIs and BMI percentiles did not significantly differ by treatment group (diet/steroids, diet, steroids; adults  $p=0.718$ ; boys  $p=0.95$ ; girls  $p=0.42$ ).

**Conclusion:** No differences in clinical characteristics of adults and children with EGIDs were observed except for the pre-diagnosis use of PPI therapy being greater in adults. The majority of adults and children had BMI/BMI percentiles within the normal range, and BMI/BMI percentiles did not differ by treatment.

**64. Determining the natural history of Alexander disease: a pilot study**

Waldman AT<sup>1</sup>, Liu G<sup>1</sup>, Lavery A<sup>1</sup>, Messing A<sup>2</sup>, Vanderver A<sup>1</sup>.

<sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA

<sup>2</sup>University of Wisconsin-Madison, Madison, WI

**Objective:** Alexander disease (AxD) is a neurodegenerative disorder caused by the accumulation of glial fibrillary acidic protein (GFAP) in astrocytes. Exciting novel studies in murine models demonstrate the ability to decrease aberrant GFAP using antisense oligonucleotide technology, offering tremendous hope for future clinical trials. However, translating these findings into effective treatments is limited by the lack of natural history studies. We sought to obtain preliminary data on disease severity to inform the selection of clinical outcome assessment tools for future prospective natural history studies in AxD.

**Methods:** We performed a retrospective chart review, supplemented by telephone interviews, for patients with AxD (classified as Type I or II disease and confirmed by genetic mutation) referred to The Children's Hospital of Philadelphia and Children's National Medical Center to determine the rate of functional decline and feasibility of gross and fine motor, speech and language, and swallowing testing in affected individuals.

**Results:** Thirty-eight patients were identified: 32 with Type I disease (mean age at symptom onset 1.5 years, range 0.3 – 3.3 years) and 6 with Type II disease (mean age at onset 27.7 years, range 14.8 – 47 years). For Type I patients, 55% were still ambulatory at a mean age of 7.3 years (range 1 – 31 years), and 83% of Type II patients were ambulatory but required an assistive device at a mean age of 36 years (range 18-57 years). Fine motor skills were not impacted for most patients: 81% of Type I and 100% of Type II patients had no or minimal functional deficits. Only 44% of Type I and 40% of Type II patients eat and drink safely and efficiently. Only 28% of Type I patients have normal receptive and expressive language, with 22% reporting inconsistent communication skills, even with close family, and 39% seldom or unable to communicate at all.

**Conclusions:** These findings support the need for performance-based outcome measures that are applicable for across the age span; capture gross motor more than fine motor deficits; assess swallowing safety, which is critical to decrease morbidity from aspiration; and characterize speech and language disorders. Based on these results, we have selected clinically relevant, robust, and quantifiable outcome measures that are currently being evaluated prospectively in a cohort of AxD patients.

# 65. A Novel Statistic for Assessing Inter-Pathologist Agreement in the Nephrotic Syndrome Study Network (NEPTUNE) Kidney Biopsy Evaluation

Jarcy Zee<sup>1</sup>, Laura Mariani<sup>1,2</sup>, Jeffrey Hodgins<sup>2</sup>, Joseph Gaut<sup>3</sup>, Matthew Palmer<sup>4</sup>,  
Lawrence Holzman<sup>4</sup>, Laura Barisoni<sup>5</sup>, Brenda Gillespie<sup>2</sup>

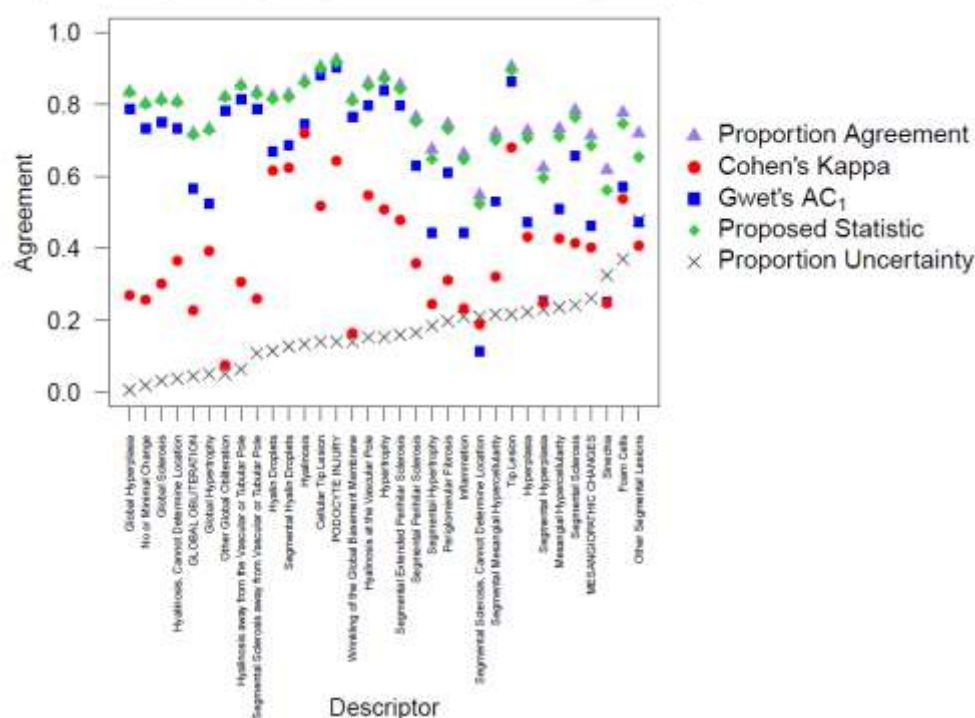
<sup>1</sup>Arbor Research Collaborative for Health, Ann Arbor, MI; <sup>2</sup>University of Michigan, Ann Arbor, MI; <sup>3</sup>Washington University, St. Louis, MO; <sup>4</sup>University of Pennsylvania, Philadelphia, PA; <sup>5</sup>University of Miami, Miami, FL

**Objective:** Reproducibility of morphologic features in nephropathology is problematic. Both Cohen's kappa and Gwet's AC<sub>1</sub> are commonly used agreement measures for dichotomous variables because they correct for chance agreement. Their calculations for the probability of chance agreement are based on assumptions that can result in widely different agreement estimates. We propose a novel agreement statistic that empirically estimates the probability of chance agreement.

**Methods:** Five pathologists rated 157 glomeruli from NEPTUNE using digital whole slide images of renal biopsies from patients with nephrotic syndrome. Sixty-five glomerular descriptors were scored on a 1-5 scale (1=absent, 2=probably absent, 3=maybe, 4=probably present, 5=present). Scores of 2-4 were considered to have some uncertainty and were thus susceptible to chance agreement. We calculated the raw proportion of agreement, Cohen's kappa, Gwet's AC<sub>1</sub> statistic, and our proposed measure.

**Results:** Among renal biopsy descriptors with 10% to 90% prevalence, we compared the different agreement measures (Figure). Cohen's kappa was generally the lowest and proportion agreement the highest. With 0% to 48% uncertainty, our proposed method was close to the raw proportion agreement and corrected more for chance agreement as the proportion of uncertainty increased.

Figure: Inter-pathologist Agreement on Renal Biopsy Descriptors



**Conclusions:** If our study pathologists are typical in having low uncertainty for rating renal biopsy descriptors, existing agreement statistics may overestimate and therefore overcorrect for the probability of chance agreement. Our proposed statistic, using raters' reports of uncertainty in each rating, may more accurately capture true inter-pathologist agreement.