



# LIPODYSTROPHY SYMPOSIUM

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## A CALL FOR GLOBAL ACTION

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**Tuesday, June 26 – Wednesday, June 27, 2018**

**ROSEN CENTRE HOTEL, ORLANDO, FL**

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**SPONSORED BY:**

Aegerion Pharmaceuticals (Novelion Therapeutics)

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Michigan Diabetes Research Center (MDRC)

Regeneron Pharmaceuticals



# SYMPOSIUM ANNOUNCEMENT

June 18, 2018

June of 2018 is a great time to reconvene the community of clinicians treating patients with lipodystrophy and patients and families afflicted with these disorders, together with researchers working on adipocyte biology, leptin action and novel metabolic therapeutics development. This year marks another milestone in the history of Lipodystrophy Syndromes as European Health Authority has released a positive opinion for approval of Metreleptin in European Union not only for generalized lipodystrophy syndromes, but also potentially for partial forms of the diseases. On the other hand, there are four new trials ongoing for treatment of familial partial lipodystrophy, three proof-of-concept studies and one larger Phase II/III global trial.

This collaborative meeting is co-hosted by the University of Michigan Metabolism, Endocrinology and Diabetes Division and Fast Forward Medical Innovation together with Lipodystrophy United, the patient foundation for lipodystrophy. We have developed our program as an ancillary event of the American Diabetes Association's Annual Meeting to take advantage of the travel time for many of our global colleagues. While we have many meeting objectives, our main goal is to bring together our vast global community of individuals living with lipodystrophy, caregivers, clinicians, researchers, and stakeholders to unify and create a path for improving the lives of those living with lipodystrophy in a way that is meaningful and measurable.

We hope to enable participation from the entire international community and work towards our dream of a global collaborative network, which we have called the SOLID Network in 2014 (Network for the Study of Lipodystrophy). In fact, we project to bring the largest number of patient members of the community this year and the broadest global scale participation of researchers and clinicians from around 4 continents

This meeting is catalyzed by two larger size educational grants from Aegerion Pharmaceuticals (now a Novelion Therapeutics company) and Regeneron Pharmaceuticals. Our other sponsors include Akcea Therapeutics and Gemphire Therapeutics. We are delighted that we can bring future funding perspectives from NIDDK. The symposium is also supported by the Michigan Diabetes Research Center (MDRC) and Metabolism, Endocrinology and Diabetes Divisions (MEND) of Michigan Medicine.

The scientific program will be opened by Dr. Louis Phillipson from University of Chicago who has dedicated his career to the study of Atypical Forms of Diabetes. Dr. Simeon Taylor and Dr. Abhimanyu Garg (UTSW) who have been pioneers in this field for the past 30 years have advised us greatly in the development of the scientific agenda and will chair the meeting. Our program features great scientists from around the world who have contributed to the field, some young colleagues and some with lifetime of experiences. We are especially honored with the participation of Dr. Gerald Shulman from Yale University who is the recipient of this year's Banting Medal at the American Diabetes Association. He will be talking about the potential for a brand new therapy for this group of diseases. The meeting will end with a keynote address by Dr. Jeffrey Friedman, the discoverer of leptin hormone, which has paved the therapeutic pathway for lipodystrophy syndromes.

The agenda is enriched by Global Perspectives and experiences, and a patient-led “Burden of Disease” Panel. Together, we will explore ways of working together and finding global solutions. Rare diseases lead to important breakthroughs in medicine, but the full potential of the treasures hiding within these gifts of nature can only be reached through collaborations across disciplines and with participation of all stakeholders.

We look forward to welcoming everyone in Orlando in 10 days.

On Behalf of Scientific Organization Committee,

Elif A. Oral, MD  
Associate Professor of Medicine  
Director, Post-bariatric Clinic  
Director, Atypical Diabetes Program  
Metabolism, Endocrinology and  
Diabetes (MEND) Division  
Department of Internal Medicine

Andra Stratton  
Co-Founder & President  
[www.lipodystrophyunited.org](http://www.lipodystrophyunited.org)  
209.845.RARE



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# DEDICATION

This program is dedicated to patients whom we have lost in the last three decades during which we worked to describe and understand various lipodystrophy syndromes. We feel lucky to have known many of them, and stood by their side as they valiantly fought their battles with the conditions. They each added to the insight we have accumulated collectively. Therefore, they will never be forgotten.

We also dedicate the work to the senior scientists who have noticed the first patients and put the disease states on the books as separate entities. The inquisitive clinical investigator is the backbone of progress in medical research, if the unusual clinical presentations do not get recognized, the mystery related to these conditions will not become a pursuit for others in the future.

With enhanced next generation sequencing tools, and big data platforms tools, we are at the brink of major breakthroughs for rare diseases. If precision medicine will become a reality, this will happen foremost in the area of rare and unusual diseases. We predict the next 5 years to be really exciting in this field and invite everyone to come along for this ride!

Scientific Organization Committee



Natalie Embry

1977 - 2017

# SCIENTIFIC ORGANIZATION COMMITTEE

**Simeon Taylor, MD, PhD**  
University of Maryland  
**Co-Chair**

**Abhimanyu Garg, MD**  
UT Southwestern Medical Center  
**Co-Chair**

**Baris Akinci, MD**  
Dokuz Eylül University

**David Araújo-Vilar, MD, PhD**  
Universidad de Santiago

**Rebecca J. Brown, MD**  
NIDDK, NIH

**Phillip Gorden, MD**  
NIDDK, NIH

**Charles F. Burant, MD, PhD**  
University of Michigan

**Ormond A. MacDougald, PhD**  
University of Michigan

**Carla Musso, MD**  
Hospital Universitario Fundación Favaloro

**Martin G. Myers, MD, PhD**  
University of Michigan

**Elif A. Oral, MD, MS**  
University of Michigan

**David Savage, MD**  
University of Cambridge

**Andra Stratton, MA**  
Lipodystrophy United

## IN COLLABORATION WITH

**Lipodystrophy United**

# SPONSORS

The University of Michigan wishes to acknowledge the following sponsors for *Lipodystrophy 2018: A Call for Global Action*:



# ACKNOWLEDGMENT

This meeting is the fourth that we have put together in the last 2 decades by a group of scientists and physicians who have been mystified by a cluster of rare diseases called the lipodystrophy syndromes. We are honored to be joined by our patient community now in the organization of these meetings and we are so much stronger for this. Hopefully as in the past meetings, those who attend our meeting "Lipodystrophy in 2018: A Call for Global Action" will see why we are so intrigued by these conditions and why we seek to understand the puzzles of these conditions!

Lipodystrophy 2018 could not have been possible without the countless hours put in by four very dedicated individuals at the University of Michigan: Diana Rus, Angie Maloney, Najoua Elbourkadi, and Julia Meireles. Diana coordinated all aspects of the meeting and Najoua provided the experienced oversight and the Michigan Medicine's FFMI infrastructure. Julia and Angie helped with logistical support. I am truly grateful for their hard work and laughter through the process (and no tears!).

I also would like to thank the rest of the administrative staff at the Metabolism Endocrinology and Diabetes Division (Sonja Highbanks, Sheila Branham and Lisa Gilbert) as they all shared in the volume of the phone calls and e-mails. Jennifer Goodwine and Allison Picinotti helped with web design, logo and agenda development as well as other PR needs. Jennifer was such a great sport despite numerous requests to revise the agenda. The Michigan Information Services is providing much needed technical support. My scientific team from the trainees to the coordinators all gave a hand, we could not do this without you Adam Neidert, Rita Hench and Rasimcan Meral. It literally takes a whole village to have a scientific meeting!

Moreover, I have to express my deep appreciation to the Aegerion Medical Affairs and Education Team and Regeneron Early Development Team for their belief and trust in the concept of this meeting. If we have a successful scientific platform today, it is because of their trust in us and commitment to the treatment of patients with lipodystrophy. Akcea Therapeutics and Gemphire Therapeutics also provided further support to the meeting. All of the members of the Scientific Organization Committee worked diligently to ensure that we reached out to the players in the field. I am especially indebted to Drs. Baris Akinci, David Araujo, Corinne Vigoroux, and Carla Musso who provided much needed scientific support and a link to their respective scientific networks. Of course, all of our distinguished speakers ignite the sparks needed to make this meeting a success.

A special thanks will go to the Lipodystrophy Board led by their visionary leader Andra Stratton who truly works tirelessly to keep the community together. Ashlei Brittany coordinated the event by providing a link to the venues and organizing all aspects of patient travel, transportation and accommodation. Linda McCormick helped to reach the broader community of lipodystrophy via emails, social media outlets and web sources.

Finally, I would like to thank all of our patients who have volunteered in the studies of lipodystrophy so willingly to enable the unlocking of some of the genetic mysteries and the development of the treatment programs at various centers for lipodystrophy and kept asking for this meeting: this meeting is put together with you and for you. You are the center of our attention!



Elif A. Oral, MD, MS  
June 18, 2018  
Ann Arbor, Michigan

# MEETING OBJECTIVES

- Get a better perspective of the current state of care delivery for lipodystrophy and to understand the burden of disease from the patient perspective
- Align the community of lipodystrophy researchers for synergy and collaboration with goals of harmonization of patient registry data elements and forming a clinical research network
- Provide an update on recent exciting findings in the lipodystrophy field
- Review and revise disease definition and to develop and publish objective disease criteria
- Identify gaps in knowledge in lipodystrophy and develop a patient-centric research agenda together with affected patient community



# AGENDA

DAY 1 – JUNE 26TH, 2018

**For Patients Only: Morning Session and Lunch will be at the Clarion Hotel.**

8:00 – 9:00 AM	Breakfast
9:00 – 11:00	<b>How to Tell Your Story</b> – Connie Newlon <ul style="list-style-type: none"><li>• Using Storytelling to Raise Awareness About LD</li></ul>
11:05 – 11:45	<b>Who Is Lipodystrophy United (LU)</b> – Andra Stratton, MA <ul style="list-style-type: none"><li>• History of Patient Foundation</li><li>• What We Do</li><li>• How LU Can Help You</li></ul>
12:00 - 1:00 PM	Lunch
1:00 – 2:15	Break and Rest
2:20	<b>Meet in Lobby to Shuttle to the Rosen Centre Hotel</b>

Scientific Meeting starts post ADA.

1:00 – 1:15 PM	<b>Welcome</b> – <i>Elif A. Oral, MD, MS; Louis Phillipson, MD, PhD; Andra Stratton, MA</i>
1:15 – 2:00	<b>Keynote Address I</b> – <i>Chair, Louis Phillipson, MD, PhD</i> <ul style="list-style-type: none"><li>• Mechanisms of Insulin Resistance in Lipodystrophy and a Potential New Therapeutic Approach – <i>Gerald Shulman, MD, PhD, Recipient of the Banting Medal 2018</i></li></ul>
2:00 – 3:30	<b>Care Models for LD: A look Around the Globe</b> – <i>Chair, Vinaya Simha, MD, MBBS and Selcuk Dagdelen, MD</i> <ul style="list-style-type: none"><li>• Japan – <i>Ken Ebihara, MD</i></li><li>• France – <i>Corinne Vigouroux, MD</i></li><li>• Learning from NHS – <i>Claire Adams, RN</i></li><li>• Spain – <i>David Araujo, MD</i></li><li>• Turkey – <i>Baris Akinci, MD</i></li><li>• Latin America – <i>Carla Musso, MD</i></li><li>• Russia – <i>Ekaterina Sorkina, MD</i></li></ul>
	<b>Role for Next Gen Sequencing in Clinical Medicine</b> – <i>Toni Pollin, PhD</i>
3:30 – 5:30	<b>The Burden of Lipodystrophy</b> – <i>Chair, Andra Stratton, MA</i> <ul style="list-style-type: none"><li>• The Impact of Metabolic Abnormalities (short overview) – <i>Carla Musso, MD</i></li><li>• The Impact of Nonmetabolic Multi-system Manifestations – <i>Claire Adams, RN</i></li><li>• Mortality in Lipodystrophy – <i>Josivan Lima, MD, PhD</i></li><li>• Living with Lipodystrophy – <i>Patient Representatives</i></li></ul>
5:45 – 6:45	<b>Poster Session, Patient Meet and Greet, and Youth Meeting (ages 11-21)</b>
7:30 – 10:00	<b>Dinner Meeting for All Attendees</b> <ul style="list-style-type: none"><li>• Tribute to Fallen Heroes – <i>Andra Stratton, MA and LU</i></li><li>• Thinking About Our Legacy – <i>Elif A. Oral, MD, MS</i></li></ul>

# AGENDA

## DAY 2 – JUNE 27TH, 2018

There will be a parallel Patient Symposium from 10:45 to 12:15.

7:00 – 7:30 AM	<b>SCIENTIFIC SESSION</b> – Breakfast – Rosen Centre Hotel
7:00 – 7:30 AM	<b>PATIENT SESSION</b> – Breakfast – Clarion Hotel
7:30 – 10:30	<b>Novel Findings in Lipodystrophy That May Change Paradigms – Chair, Justin Rochford, PhD</b> <ul style="list-style-type: none"><li>• Mechanisms Underlying Lipodystrophy and Potential Therapies: A View from the Lab – <i>Justin Rochford, PhD</i></li><li>• Seipin and Brain: Lessons from Celia's Encephalopathy – <i>David Araujo, MD, PhD</i></li><li>• MFN2: Crossroads Between White and Brown Fat – <i>Corinne Vigouroux, MD</i></li><li>• Laminopathies: A Personal Basic Science Perspective – <i>Sonia Rehal, PhD</i></li><li>• Cardio-metabolic Assessment of Lamin A/C Gene Mutation Carriers: A Phenotype-Genotype Correlation – <i>Marie-Christine Vantyghem, MD, PhD</i></li><li>• Animal Models of Lipodystrophy – <i>Anil Agarwal, PhD</i></li><li>• Novel Mechanisms in Lipodystrophy – <i>Abhimanyu Garg, MD</i></li></ul>
10:30 – 10:45	Break
10:45 – 12:20 PM	<b>PATIENT SESSION</b>  <b>Road Map to Novel Therapies I – Chair, Simeon Taylor, MD, PhD</b> <ul style="list-style-type: none"><li>• Overview – <i>Simeon Taylor, MD, PhD</i></li><li>• Summary of Leptin Studies – <i>Rebecca Brown, MD, MHS</i></li><li>• Beyond Leptin: Ongoing Trials – <i>Elif A. Oral, MD, MS</i></li><li>• A Look to the Horizon – <i>Simeon Taylor, MD, PhD</i></li></ul>
10:45 – 12:15 PM	<b>PATIENT SESSION</b>  <b>Be Your Best Advocate – LU Board Member</b> <ul style="list-style-type: none"><li>• Work with a Care Team to Get the Care You Need</li><li>• Tools to Help You Manage and Track Your Health</li><li>• How Can You Help LU</li></ul>
12:15 – 12:30	Break
12:30 – 1:45	<b>Lunch Meeting – Chair, Elif A. Oral, MD, MS</b> <b>Objective Disease Criteria: Is This an Attainable Goal and What Do We Have to Do?</b> <ul style="list-style-type: none"><li>• Data from Michigan and NIH – <i>Rasimcan Meral, MD</i></li><li>• Open Discussion</li></ul>
2:00 – 3:30	<b>The Need for Change in Disease Classifications</b> <ul style="list-style-type: none"><li>• Case Presentations That Challenge Current Paradigm – <i>Cases from across the globe</i></li></ul> <b>All About Disease Registries – Chair, David Araujo, MD, PhD</b> <ul style="list-style-type: none"><li>• LD Lync: New Registry for Sharing Data – <i>Baris Akinci, MD</i></li><li>• European Registry – <i>David Araujo, MD, PhD</i></li><li>• Current Efforts in Latin America – <i>Renan Montenegro, Jr., MD; Maria E. Andres, MD; Virginia Fernandes, MD; Nelson Purizaca, MD</i></li><li>• Discussion on Data Harmonization – <i>Open Forum for All Attendees</i></li></ul>
3:30 – 4:15	<b>Road Map to Novel Therapies II – Chair, Rebecca Brown, MD</b> <ul style="list-style-type: none"><li>• Metabolic Surgery for Lipodystrophy – <i>Audrey Melvin, MB, BCh</i></li><li>• Genomic Approaches to Lipodystrophy: From Novel Gene Discovery to Precision Health – <i>Alan Shuldiner, MD</i></li></ul>
4:15 – 5:15	<b>Keynote Address II – Chair, Abhimanyu Garg, MD</b> <ul style="list-style-type: none"><li>• Leptin, Lipodystrophy, and Neural Regulation of Glucose Metabolism – <i>Jeffrey Friedman, MD, PhD</i></li></ul>
5:30	<b>Symposium Adjourns</b>

# BIOGRAPHIES

## Claire Adams, RGN, MCLinRES, PGCert, PScHons

Senior Research Nurse & Specialist Nurse

University of Cambridge Metabolic Research Laboratories

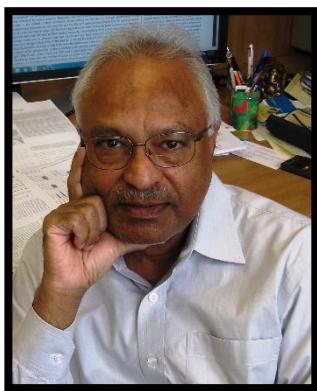


Claire Adams is a specialist and research nurse working in the Severe Insulin Resistance Team and Institute of Metabolic Science, University of Cambridge, UK. Claire has worked with Professor Savage since 2007 supporting people living with lipodystrophy in research studies and clinical care. She is particularly interested in the psychological impact of lipodystrophy and how we can improve support. Claire is also a trustee for Lipodystrophy UK.

## Anil Agarwal, PhD

Professor of Internal Medicine

UT Southwestern Medical Center



Dr. Agarwal earned his doctoral degree while working at Central Drug Research Institute, Lucknow, India and further training at the Population Council, The Rockefeller University and Cornell Medical College, New York. Dr. Agarwal has been studying the molecular genetics and biology of rare diseases which includes juvenile hypertension (Apparent Mineralocorticoid Excess) and various types of lipodystrophies. Chief among these were AGPAT2, PPAR $\gamma$ , ZMPSTE24 and PSMB8. Dr. Agarwal also developed an animal model of lipodystrophy to study the pathophysiology of lipodystrophy and its associated clinical phenotype. Dr. Agarwal has published his research findings in leading peer reviewed journals which includes Nature Genetics, Cell Metabolism, PNAS, JBC, JLR and JCEM.

## Baris Akinci, MD

Professor of Medicine

Dokuz Eylul University, Turkey

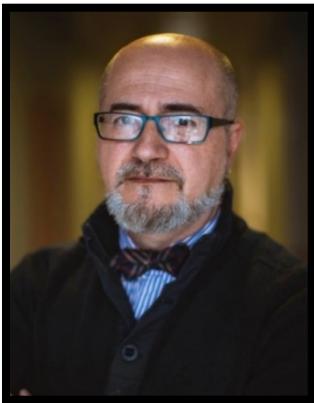


Dr. Akinci received his M.D. degree from Ege University. He completed his residency in Internal Medicine and his fellowship in Endocrinology at Dokuz Eylul University. Dr. Akinci worked as a postdoc researcher under supervision of Dr. Abhimanyu Garg in UT Southwestern, Dallas in 2011-2012. Dr. Akinci is the founder of the Turkish Lipodystrophy Study Group. His research focuses on the natural history of lipodystrophy, and the link to metabolic abnormalities, and end-organ complications. Dr. Akinci is a faculty member of the Division of Endocrinology at Dokuz Eylul University. As a Fulbright Scholar, Dr. Akinci is currently working with Dr. Elif Oral at the University of Michigan.

**David Araújo-Vilar, MD, PhD**

Professor of Medicine

University of Santiago de Compostela, Spain



David Araújo-Vilar is a professor of medicine at the School of Medicine in Santiago de Compostela, Spain, and a senior consultant in endocrinology and nutrition at the University Clinical Hospital of Santiago de Compostela. He earned his medical and doctorate degrees at the Universidad de Santiago de Compostela and completed postgraduate training at Oxford University in the United Kingdom and Galicia General Hospital in Spain. Dr. Araújo-Vilar's research centers on the genetic basis of rare lipodystrophic syndromes and severe insulin resistance syndromes. He is the president of the Spanish Lipodystrophy Society and sits on the executive board of the European Consortium of Lipodystrophies.

**Graham Brady, MD, PhD**

Clinical Lecturer in Internal Medicine

University of Michigan Medical School



Dr. Brady is a physician and scientist in the Division of Gastroenterology and Hepatology at the University of Michigan. He received his undergraduate degree from Duke University and his MD and PhD degrees from the University of Michigan Medical School. His clinical interests lie in the diagnosis and management of chronic liver disease, including nonalcoholic fatty liver disease (NAFLD). His research interests include the genetics and mechanisms of NAFLD, with particular emphasis on the roles of the nuclear lamina and lamina-associated proteins in liver disease.

**Rebecca J. Brown, MD, MHSc**

Lasker Clinical Investigator

NIDDK, NIH



Dr. Rebecca Brown graduated from Rice University and Mayo Medical School, and completed pediatric residency at Rainbow Babies and Children's Hospital. In 2005, she came to the National Institutes of Health for fellowship in pediatric endocrinology, and she has remained in the NIH intramural research program since that time. In 2015, she became the first Lasker tenure track investigator in NIDDK. Her research focuses on pathophysiology and clinical therapeutics for rare disorders of extreme insulin resistance, including lipodystrophy and dysfunction of the insulin receptor, as well as the mechanisms of action of leptin in improving metabolic disease.

**Selcuk Dagdelen, MD**

Professor of Medicine

Hacettepe University, Turkey



Dr. Selcuk Dagdelen is a Professor of Endocrinology and Metabolism in Hacettepe University, Ankara, Turkey. He received his medical degree from Hacettepe University and has been in practice for more than 20 years. Dr. Dagdelen has a special interest in diabetes and rare metabolic diseases. Dr. Dagdelen leads the Turkish Endocrine Society's Rare Disease Study Group.

**Ken Ebihara, MD, PhD**

Associate Professor of Medicine

Jichi Medical University, Shimotsuke, Japan



Dr. Ebihara obtained his M.D. in 1994 from Tohoku University in Sendai, Japan. In 1996, Dr. Ebihara joined Prof. Kazuwa Nakao's lab at Kyoto University in Kyoto, Japan and started his leptin study. He obtained a Ph.D. in 2000. Since then, he has been studying leptin and lipodystrophy. In 2002, he first started leptin therapy in patients with lipodystrophy in Japan. From 2009, he was an associate professor in Translational Research Center, Kyoto University Hospital. In 2014, he moved to the Division of Endocrinology and Metabolism, Jichi Medical University in Shimotsuke, Japan as an associate professor.

**Virgínia Fernandes, MD, PhD**

Adjunct Professor of Medicine

Faculty of Medicine at Universidade Federal do Ceará



Prof. Virgínia Fernandes is researcher of the National Institute of Science and Technology for Obesity and Diabetes (INCT/CNPq). Her main research areas of interest are lipodystrophies, clinical diabetes, dyslipidemia, and insulin resistance. She is the medical coordinator of the reference clinics for multidisciplinary care of lipodystrophic patients in Ceará, Brazil, and member of the Brazilian Group for the Study of Inherited and Acquired Lipodystrophies (BRAZLIPO). This project is a National Network for the Study and Registry of Brazilian Lipodystrophy Cases, aiming to establish clinical and research partnerships, providing better understanding of the natural history of the disease, and patients care.

## **Maria Cristina Foss-Freitas, MD, PhD**

Associate Professor

Sao Paulo University - Ribeirao Preto Medical School



Dr. Foss-Freitas graduated in medicine in 1997, specialized in Endocrinology in 2001 and concluded her PhD in Medicine from the University of São Paulo in 2004. During the period of 2009 and 2010 she was a postdoctoral fellow in Joslin Diabetes Center where she improved her skills in basic and clinical research. Currently she is an associate professor in the Department of Internal Medicine, Divisions of Endocrinology and Metabolism and Nutrition Sao Paulo University. She has been working in research and clinical assistance in various scenarios and her highest interest is in the following subjects: diabetes mellitus, immunology and lipodystrophies.

## **Jeff Friedman MD, PhD - Keynote Lecturer**

Marilyn M. Simpson Professor, The Rockefeller University

Investigator, Howard Hughes Medical Institute



Dr. Jeffrey Friedman is a physician scientist studying the genetic mechanisms that regulate body weight. Dr. Friedman's research on various aspects of obesity received national attention in late 1994, when it was announced that he and his colleagues had isolated the mouse ob gene and its human homologue. They subsequently found that injections of the encoded protein, leptin, decreases body weight of mice by reducing food intake and increasing energy expenditure. Current research is aimed at understanding the genetic basis of obesity in human and the mechanisms by which leptin transmits its weight-reducing signal.

## **Abhimanyu Garg, MD**

Professor of Internal Medicine

UT Southwestern Medical Center



Abhimanyu Garg, M.D. is Professor of Internal Medicine and Chief, Division of Nutrition and Metabolic Diseases at UT Southwestern. He is Director of Lipid Services at Parkland Memorial Hospital and UT Southwestern. He holds a Distinguished Chair in Human Nutrition Research. He has been evaluating patients with various types of lipodystrophies for over 30 years. He has carefully characterized the clinical and metabolic features of various types of lipodystrophies, including reporting of novel syndromes. He has used the state of the art genetic technology to discover many novel genes, such as, AGPAT2, PPARG, ZMPSTE24, PSMB8, and ADRA2A for these disorders.

**Josivan Lima, MD, PhD**

Professor of Endocrinology

Hospital Universitário Onofre Lopes

Universidade Federal do Rio Grande do Norte (UFRN), Natal, RN, Brazil



Josivan Lima holds a degree in Medicine (1995) and a doctorate in Health Sciences (2016) from the Federal University of Rio Grande do Norte. He has specialized in Endocrinology at Agamenon Magalhães Hospital in Recife/PE, Brazil (1996-1997) and City Hospital, Nottingham/UK (1998). He was general secretary of the Brazilian Society of Endocrinology from 2009 to 2012. Dr. Lima is a professor of endocrinology at the Onofre Lopes University Hospital (Natal, Brazil) since 2004, and published 30 articles in international journals, mainly in the area of diabetes, dyslipidemia and metabolic syndrome. His work focuses on congenital generalized lipodystrophy, and he has followed more than 40 patients.

**Audrey Melvin, MB, BCh, MRCPI**

Postdoctoral Fellow

National Severe Insulins Resistance Service, Cambridge, UK

Metabolic Research Laboratory, University of Cambridge, Cambridge, UK

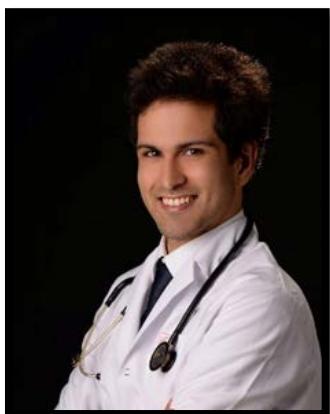


In her current role as a clinical research fellow Audrey is working at the National Severe Insulin Resistance Service, Cambridge, UK she is engaged in the delivery of care to individuals affected by lipodystrophy. Audrey is undertaking her doctoral studies at the Metabolic Research Laboratory, University of Cambridge under the supervision of Prof Sir Stephen O'Rahilly where her work focuses on the role of PPAR alpha receptors in human metabolism. She is particularly interested in novel therapies in the prevention and management of the metabolic complications associated with lipodystrophy.

**Rasimcan Meral, MD**

Postdoctoral Research Fellow

University of Michigan



Rasimcan Meral graduated from Istanbul Faculty of Medicine in 2016 to pursue a career in research at the University of Michigan as a postdoc. He developed an interest in lipodystrophy after meeting Dr. Elif A. Oral as a student in 2012. His current research focuses on developing diagnostic algorithms for lipodystrophy syndromes using Dual Energy X-ray Absorptiometry and image analysis and investigation of cardiac phenotypes in patients with rare laminopathies using induced pluripotent stem cell models.

**Renan Montenegro Jr, MD, PhD**

Associate Professor of Medicine

Faculty of Medicine at Universidade Federal do Ceará



Prof. Renan Montenegro Jr is researcher of the National Council for Scientific and Technological Development and member of the National Institute of Science and Technology for Obesity and Diabetes (INCT/CNPq). His main research areas of interest are clinical diabetes, dyslipidemia, and lipodystrophies. Prof. Montenegro's implemented a reference center for multidisciplinary care for lipodystrophic patients and created the Brazilian Group for the Study of Inherited and Acquired Lipodystrophies (BRAZLIPO), a National Network for the Study and Registry of Brazilian Lipodystrophy Cases, aiming to establish clinical and research partnerships, providing better understanding of the natural history of the disease, and patients care.

**Carla Musso, MD**

Endocrinologist

Chief of Diabetes Division Favaloro Foundation



Chief of Diabetes Division at Favaloro Foundation  
and Medical Staff of the Endocrinology and Metabolism

Department Unidad Asistencial Dr. C Milstein. Carla spent 3 years (2003-2005) at NIH working in the metreleptin protocol with lipodystrophy patients. Back in Argentina, she kept involved with the protocol and sent 6 patients to be accepted. Carla got the compromise with the disease and helped to spread knowledge of it in Argentina. Carla coordinates the diabetes department of the Argentinean society of endocrinology and at the Obesity and Diabetes department of Argentinean society of Diabetes.

**Elif A. Oral, MD, MS**

Associate Professor of Medicine

University of Michigan



Dr. Oral completed her medical education in her home country of Turkey at the University of Istanbul. In 1996, she completed her residency in Internal Medicine at Sinai Hospital of Detroit (Michigan). She then pursued a Fellowship in Endocrinology, Metabolism and Diabetes at the NIDDK. She joined the University of Michigan in 2002. She is promoted to full professor this spring, with title effective September 2018. Her research focuses on the importance of adipocytes in human metabolism. She is best known for her work showing the remarkable efficacy of leptin in rare lipodystrophy syndromes leading to the approval of Metreleptin in 2014 by the FDA. Dr. Oral leads a multidisciplinary team investigating novel therapies for lipodystrophy syndromes and also performing next generation sequencing to define novel forms of the diseases.

**Toni Pollin, MS, PhD, CGC**

Associate Professor of Medicine and Epidemiology & Public Health  
University of Maryland School of Medicine



Toni Pollin is a genetic counselor, researcher, and educator at the University of Maryland School of Medicine, where she is an Associate Professor of Medicine and Epidemiology & Public Health and Leader for the PhD and MS program in Human Genetics. Her research focuses on the elucidation of genetic contributions to common, complex diseases, particularly diabetes, and on addressing the opportunities and challenges in the real world implementation of genomic medicine. Dr. Pollin earned her MS in Cellular Developmental Biology and Genetics/Genetic Counseling at the University of Minnesota and completed her PhD in Human Genetics at University of Maryland Baltimore.

**Nelson D. Purizaca, MD**

Resident in Medical Genetics  
Cayetano Heredia Peruvian University



Nelson Purizaca was born in Piura, Peru. He graduated as a Medical Doctor from the National University of Piura, and currently performs his Specialty in Medical Genetics in Cayetano Heredia Peruvian University, Lima – Peru. He started his research on Berardinelli-Seip Syndrome in a rural village from Piura, Peru. With the help of researchers of the International Registry of Werner Syndrome, University of Washington, they described a new genetic variant that causes this disease. Currently, he investigates the epidemiological and clinical aspects of SBS in Peruvian patients, in addition to the relation between the migration due to natural phenomena and the distribution of this disease.

**Sonia Rehal, MSc, PhD**

Postdoctoral Researcher  
Memorial Sloan Kettering Cancer Center, NY



Sonia Rehal received her undergraduate training at McGill University (physiology) and her graduate training at the University of Calgary (physiology). She is currently pursuing a postdoctoral fellowship at Sloan Kettering Cancer Center, studying the mechanisms of vascular dysfunction in obesity. Furthermore, Sonia Rehal has partial lipodystrophy (FPLD2). Her sister and mother were taken away by this disease and she herself suffers with medical issues. An unexhaustive medical history includes diabetes, dyslipidemia, hypertension, atrial fibrillation, history of stroke and heart attack and an implantable cardiac device. She is a key example of how laminopathies can affect a multitude of organs systems.

**Justin Rochford, BSc, PhD**

Reader in Metabolic Health

Rowett Institute, University of Aberdeen, UK



Dr. Justin Rochford is a Reader in Metabolic Health at the Rowett Institute, University of Aberdeen. He trained at Newcastle University, UK and INSERM U145 in Nice, France before working with Prof. Sir Steve O'Rahilly at the University of Cambridge, UK. He subsequently held a British Heart Foundation Intermediate Fellowship and an MRC New Investigator Research Grant and developed an independent research program investigating adipocyte development. In 2013 he moved to the Rowett Institute in Aberdeen where he leads a group studying the molecular basis of diseases featuring altered adipose tissue development and function.

**Alan R. Shuldiner, MD**

Vice President Regeneron Genetics Center

Regeneron Pharmaceuticals, Inc.



A leading national expert and researcher in personalized medicine, Dr. Shuldiner focuses on the genetics of age-related diseases, including type 2 diabetes, obesity, osteoporosis, and cardiovascular disease. He is best known for his studies involving Old Order Amish, a homogeneous population ideal for genetic studies. Dr. Shuldiner serves as vice president at the Regeneron Genetics Center, a program that focuses on early gene discovery and functional genomics and facilitates drug development. He serves on several steering and advisory committees related to his expertise in complex disease genetics and the translation of genetic discoveries to the clinical setting.

**Gerald I. Shulman, MD, PhD – Keynote Lecturer**

George R. Cowgill Professor of Medicine and Cellular &amp; Molecular Physiology

Yale University, Howard Hughes Medical Institute



Dr. Shulman is an Investigator of the Howard Hughes Medical Institute and the George R. Cowgill Professor of Medicine and Cellular & Molecular Physiology at Yale University. He is also Co-Director of the Yale Diabetes Research Center. Dr. Shulman has pioneered the use of magnetic resonance spectroscopy to non-invasively examine intracellular glucose and fat metabolism in humans that have led to several paradigm shifts in our understanding of type 2 diabetes. Dr. Shulman has been elected to the National Academy of Medicine, the American Academy of Arts and Sciences and the National Academy of Sciences.

**Vinaya Simha, MBBS, MD**

Assistant Professor, Department of Internal Medicine  
Mayo Clinic



Dr. Vinaya Simha, MBBS, MD is a Consultant in the Division of Endocrinology, and Assistant Professor, Department of Internal Medicine at Mayo Clinic, Rochester, MN. He completed his medical school and post-graduation in human physiology in India before coming to the United States for further training. He completed his Fellowship training in Endocrinology, and in Nutrition and Metabolic Diseases at UT Southwestern Medical Center, Dallas. He served on the faculty at UT Southwestern and in Texas Tech University Health Sciences Center before moving to Mayo Clinic in 2012. He is board certified in Internal Medicine, Endocrinology and Clinical Lipidology.

**Ekaterina Sorkina, MD, PhD**

Research Assistant at Clamp-technologies laboratory  
Endocrinology Research Centre, Moscow, Russia



Ekaterina Sorkina, MD, PhD is endocrinologist and research assistant at the Clamp-technologies laboratory, Institution of Diabetes, Endocrinology Research Center in Moscow, Russia. She is a member of many Russian and international professional society and the ambassador of European Young Endocrine Scientists in Russia. Her scientific interest covers endocrinology and genetics, lipodystrophies (inherited and acquired), laminopathies, inherited forms of diabetes mellitus and insulin resistance. She is the author of 22 publications, 5 of them quoted on Pubmed. She is also a member of European Consortium on Lipodystrophies (ECLip) and a member of the ECLip registry board.

**Andra Stratton, MA**

Co-Founder & President of Lipodystrophy United



Andra Stratton is a patient with Familial Partial Lipodystrophy (FPL) and the Co-Founder & President of Lipodystrophy United. She has led the efforts to increase awareness and support among patients for all types of lipodystrophy around the world since her diagnosis and LU's inception in 2012. Andra works closely with lipodystrophy stakeholders and has been the patient voice in meetings and conferences with lipodystrophy experts in the United States and Europe. In addition to her work in Lipodystrophy, Andra is a recognized lead advocate as a Global Genes Rare Leader, a member of Rare Advocacy Movement and the host for Rare In Common.

**Simeon I. Taylor, MD, PhD**

Professor of Medicine

University of Maryland School of Medicine



As Chief of NIDDK's Intramural Diabetes Branch, Dr. Taylor's research focused on genetics of insulin resistant diabetes and investigations of innovative therapies including metreleptin to treat lipodystrophy. He moved to the pharmaceutical industry in 2000. As Vice President of Cardiovascular and Metabolic Disease Research at Bristol-Myers Squibb, he contributed to R&D leading to saxagliptin, dapagliflozin, metreleptin, and apixaban. He returned to academia in 2013 where he serves as Professor of Medicine and Director of the Mid-Atlantic Nutrition Obesity Research Center at the University of Maryland School of Medicine. His current research relates to pharmacogenetics and clinical safety of diabetes drugs as well as the genetics of cardiometabolic disease.

**Cynthia Melissa Valerio, MD, MSc**

Medical Research and Head of Metabolism Unit

Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE)



Undergraduated from Medical School at Pontifícia Universidade Católica do Paraná, Cynthia completed residency in Internal Medicine at Hospital das Clínicas of Federal University of Paraná and further specialized in Endocrinology and Metabolism at Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE). She received M.Sc Degree in Internal Medicine from Federal University of Rio de Janeiro with master's thesis study of body composition in familial partial lipodystrophies. Currently she is head of Metabolism Unit and medical researcher in Instituto Estadual de Diabetes e Endocrinologia and chair of the Department of Dyslipidemia and Atherosclerosis of the Brazilian Society of Endocrinology and Metabolism.

**Marie-Christine Vantyghem, MD, PhD**

Professor of Endocrinology, Diabetes and Metabolism

Lille University Hospital, France



Prof Vantyghem received her specialty trainings at the University of Lille, France. In 2009, she obtained a clinical research contract with the INSERM U1190, devoted to "Translational Research in Diabetes." Her main research areas are islet transplantation and lipodystrophies with a cohort of about 200 LD patients investigated. A biobank has been organized under the name project PHRC (Hospital Project for Clinical Research) IL7 lipodystrophies. Lille University Hospital belongs to FIRENDO, a French network for rare endocrine diseases. In this network, Dr. Vantyghem is more especially involved in PRYSIS reference center headed by Prof Vigouroux. She collaborates to the European Consortium for Lipodystrophies (ECLIP).

**Corinne Vigouroux, MD, PhD**

Professor of Medicine

Saint-Antoine University Hospital, France



Prof Corinne Vigouroux is an endocrinologist and a molecular and cellular biologist working at Saint-Antoine University Hospital, Assistance-Publique Hôpitaux de Paris, France. She has been involved for many years in translational research on molecular biology, pathophysiology, diagnosis and patient care in the field of lipodystrophies and insulin resistance syndromes. She is the coordinator of the French National Reference network for "Rare Diseases of Insulin Sensitivity and Insulin Secretion" and the leader of the research group "Genetic Lipodystrophy" at Saint-Antoine Research Center, Sorbonne Medical University, Paris.

# SPEAKER ABSTRACTS

## **The Impact of Non-Metabolic Multi-System Manifestations**

*Claire Adams, RGN, MCLinRES, PGCert, PScHons*

Patients with lipodystrophy have highlighted that the psychological effects of the condition can be as challenging as the metabolic consequences. However, there is a paucity of published information about the psychological impact of lipodystrophy or the prevalence of mental health disorders within this patient group. Initially we conducted a qualitative study within the SIR Service exploring body image in lipodystrophy which confirmed observations in clinical practice, that lipodystrophy can contribute to a negative body image. Following this we undertook a retrospective review of patients attending our Severe Insulin Resistance Service, this highlighted that 40% of patients were prescribed antidepressants this compares to between 10-20% in the General Type 2 Diabetes setting. Currently there are limited options available to help support patients with the psychological impact of lipodystrophy. We are currently working alongside patients to develop support for negative body image.

## Mouse Models of Lipodystrophy: Unexpected Observations

Anil Agarwal, PhD

Division of Nutrition and Metabolic Diseases, Department of Internal Medicine & Center for Human Nutrition,  
University of Texas Southwestern Medical Center, Dallas, TX-75390

To study the molecular pathway(s) involved in causing lack of body fat as a consequence of mutations in various genes, mouse models have been generated by the homologous gene deletion approach. Interestingly, some of these mouse models of lipodystrophy yielded unexpected results. For example, while biallelic *BSCL2* mutations in humans lead to near total loss of adipose tissue, *Bscl2*<sup>-/-</sup> mice had partial preservation of adipose tissue, indicating a differential role of *BSCL2* in the humans and mice. The *Agpat2*<sup>-/-</sup> mice on the other hand had near total loss of body fat and suggested the possibility of upregulation of an alternate pathway for synthesis of triglycerides in liver (Mogat1 pathway). However, double knock-out, *Agpat2*<sup>-/-</sup>/*Mogat1*<sup>-/-</sup> mice did not reveal any amelioration of severe hepatic steatosis seen in the *Agpat2*<sup>-/-</sup> mice. The *Agpat2*<sup>-/-</sup> mice, paradoxically, also have elevated levels of hepatic phosphatidic acids which may be activating hepatic gluconeogenesis. The knock-out of *Agpat1*, which is closely related to *Agpat2*, revealed an altogether unexpected phenotype. *Agpat1*<sup>-/-</sup> mice were hypoglycemic, had audiogenic seizures, and reproductive abnormalities. Lastly, mutations in the proteins localized in the caveolae, like caveolin 1 (CAV1) and polymerase I transcript releasing factor (PTRF) also resulted in human CGL. New observations suggest that each of these proteins might have a caveolae-independent function. In fact, a recent study suggests that PTRF is localized to the nucleus where it transcribes ribosomal DNA (rDNA), a main component for protein synthesis. These mouse models of lipodystrophies reveal novel functions of these proteins in adipocyte biology.

## Care Models for LD: A Look Around the Globe

*Baris Akinci, MD*

Division of Endocrinology and Metabolism, Dokuz Eylul University, Izmir, Turkey.

Fulbright Scholar at Brehm Center for Diabetes Research and Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI, USA.

The Turkish Lipodystrophy Study Group (TuLip) is a national platform which is committed improving knowledge on lipodystrophy syndromes by bringing together physicians taking care of such patients. It registers patients with lipodystrophy, and provides genetic testing. The group is now established under the Rare Disease Study Group of the Turkish Endocrine Society. The TuLip registry includes more than 150 patients with lipodystrophy. Our previous studies identified several novel mutations causing lipodystrophy in the Turkish population. The group studied the natural history and disease burden of various subtypes of generalized and partial lipodystrophy. Results of first metreleptin treatment for generalized lipodystrophy in Turkey were reported. Our current efforts focus on determining the characteristics of end-organ complications in patients with lipodystrophy and investigating the cellular and molecular mechanisms of adipose tissue loss.

## All About Disease Registries: LD Lync: New Registry for Sharing Data

*Baris Akinci, MD*

Division of Endocrinology and Metabolism, Dokuz Eylul University, Izmir, Turkey.

Fulbright Scholar at Brehm Center for Diabetes Research and Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI, USA.

Rare disease registries are an important tool to improve knowledge, to understand the natural history of the disease, and to determine the effects of different interventions. Our national registry helped us improve our service to the lipodystrophy community. Now, the University of Michigan launches the LD-Lync study, a new registry for sharing data. The LD-Lync is an international, prospective, multicenter study of lipodystrophy. The study targets to recruit a total of 500 participants with lipodystrophy simultaneously at various clinical centers. This registry will help clinicians, scientists and patients to predict the specific natural history of various subtypes of genetic lipodystrophies, will allow easier assessment of the clinical value added via novel therapeutics, and may lead to targeted novel therapeutic interventions.

## European Lipodystrophy Registry (ECLip Registry)

David Araujo-Vilar, MD, PhD

David Araujo-Vilar<sup>1</sup>, Julia von Schnurbein<sup>2</sup>, Martin Wabitsch<sup>2</sup>

1. University of Santiago de Compostela, Spain; 2. University of Ulm, Germany

Given the lack of knowledge on lipodystrophies, the medical and social responsibility for the persons affected by it calls for the monitoring of the progression over long periods of time. Sensible clinical and basic research into rare diseases such as lipodystrophy is only possible in multilocation networks with sufficient case numbers. Also, reliable information on the incidence of certain manifestation patterns, health status, etc. is of utmost importance for health care and health policy in these rare diseases.

Therefore, the European Consortium of Lipodystrophies (ECLip), an association of European experts on lipodystrophy, has launched a registry for lipodystrophies which is committed to help to improve the research conditions by consolidating this kind of information. Seventeen public centers from 10 European countries are involved in it. The registry is hosted at Ulm University using the Open Source Software OSSE (Open Source Registry System for Rare Diseases in the EU), which is a web based platform focused on a federated approach that allows to perform distributed searches which are designed to comply data protection requirements and preserve data sovereignty.

The aim of the registry is to compile data on the natural history of each different sub-group of lipodystrophies, their comorbidities, treatment options used and medical and quality of life outcome for the patients.

*The registry has been registered at ClinicalTrials.gov (Identifier: NCT03553420).*

## Seipin and Brain: Lessons from Celia's Encephalopathy

David Araujo-Vilar, MD, PhD

Seipin is an endoplasmic reticulum resident protein encoded by *BSCL2* gene, expressed predominantly in brain and testes. Although seipin is playing a critical role in lipid droplets biogenesis, its function is not yet completely understood, particularly in brain. In order to shed light over this issue, the expression of *BSCL2* transcripts in the central nervous system (CNS) of humans was studied, together with the effect of their overexpression on a neuron model and its relationship with oxidative stress protection, as well as to try to better understand the pathogenic mechanisms of Celia's Encephalopathy (PELD). Using qPCR in samples across the brain regions of subjects who underwent forensic autopsy and from a case with Celia's Encephalopathy *BSCL2* transcripts were analyzed. The transcript encoding the long seipin isoform (*BSCL2*-203, 462 aa) was expressed primarily in the brain and its expression was inversely correlated with age in the temporal lobe, amygdala, and hypothalamus. Strong positive correlations were found between *BSCL2* expression and some genes encoding protective enzymes against oxidative stress including *SOD1* and *SOD2*, as well as *PPARG* and *CAT* in the amygdala. These results were experimentally corroborated by overexpressing *BSCL2* transcripts in SH-SY5Y cells and assessing their effects on neuron differentiated cells. Confocal microscopy studies showed that both seipin and PEX16, a peroxisome cover protein, were closely expressed in the hypothalami of healthy human brains, and PEX16 was absent in the same region of the PELD case. We hypothesize that seipin has specific CNS functions related to oxidative stress protection and may play a role in peroxisome biogenesis.

## Summary of Leptin Studies

*Rebecca J. Brown, MD, MHSc*

Leptin is an adipocyte derived hormone that is present in proportion to fat mass, and serves as a signal of the body's energy reserves. In physiologic states of leptin deficiency, such as starvation, and pathophysiologic states, such as leptin gene mutations, low leptin is sensed as a starvation signal and leads to hyperphagia. Lipodystrophy syndromes, in which adipose tissue is deficient, are an example of a leptin deficient state. These syndromes are further complicated by ectopic lipid deposition, leading to severe insulin resistance, diabetes, dyslipidemia, and non-alcoholic fatty liver disease. In patients with generalized lipodystrophy, metreleptin leads to dramatic improvements in ectopic lipid, insulin resistance, glycemia, and hypertriglyceridemia. Improvements in blood glucose and triglycerides are seen as early as one week of therapy, and are maintained over long-term follow-up of 3-5 years. In patients with partial lipodystrophy, who have preservation of some fat depots and hence less severe leptin deficiency, metreleptin leads to more variable metabolic improvements, with the greatest benefit seen in patients with lower endogenous leptin and more severe metabolic disease. Based on uncontrolled studies of metreleptin treatment in patients with lipodystrophy syndromes, metreleptin is approved in the US for treatment of generalized lipodystrophy, in Japan for treatment of both generalized and partial lipodystrophy, and EU approval is anticipated.

## Current State and Issues of Lipodystrophy in Japan

*Ken Ebihara, MD, PhD*

In Japan, the clinical trial of metreleptin in patients with lipodystrophy was started in 2002.

In 2013, metreleptin was approved for not only generalized lipodystrophies but also partial ones in Japan. This is the first approval in the world. While the metreleptin got a high price (11.3mg vial is over \$300), lipodystrophy was designated as the intractable diseases for free medical care by Ministry of Health, Labour and Welfare in 2015. This subsidy program was started in 1972 with 56 diseases and was expanded to cover 330 diseases including lipodystrophy to date. At the designation of lipodystrophy in this program, tentative diagnosis criteria and severity classification was set up. Survey slips according to these criteria and classification is used for the notification system of this program. In the future, we will aggregate and analyze data periodically in cooperation with Ministry of Health, Labour and Welfare. In addition, the establishment of the practice guideline for lipodystrophy was selected as one of the high--priority issues by The Japan Endocrine Society in 2015. A working group was organized and the task is currently in progress. However, the task was riddled with problems such as a broad range of etiology and pathology on lipodystrophy. In this symposium, I will introduce you our current state and issues of lipodystrophy in Japan.

## **All About Disease Registries: Current Efforts in Latin America - BRAZLIPO**

*Virgínia Fernandes, MD, PhD,<sup>1</sup> Renan Montenegro Jr, MD, PhD<sup>1</sup>*

<sup>1</sup>Faculty of Medicine at Universidade Federal do Ceará

Disease Registry is an important task to establish strategies for health care. However, in rare diseases as lipodystrophies (LD) it would be a challenge, especially in continental countries like Brazil. LD have a global prevalence of approximately 1.3-4.7 cases/million. In generalized cases, that number is even lower (0.2-1.0 cases/million). Since its first description by W. Berardinelli until current literature records, we have approximately 500 cases of congenital generalized LD described worldwide and around 150 cases identified in Brazil. However it is possible that factors like the lack of knowledge about LD, absence of **clinical** practice guidelines as well as the high prevalence of undernutrition in our country hinder their correct diagnosis and then adequate patients care. Thus a group of clinical researchers working in reference centers for patients with LD in Brazil created The Brazilian Group for the Study of Inherited and Acquired Lipodystrophies (BRAZLIPO - [www.brazlipo.org](http://www.brazlipo.org)) with the support of the Dyslipidemia and Atherosclerosis Department of the Brazilian Society of Endocrinology and Metabolism. BRAZLIPO is a National Network that aims the integration of physicians that lead with LD, registry of Brazilian lipodystrophy cases and development of strategies to improve their clinical care. This network would allow us to share relevant data, establish research partnerships, provide evidence to clinical practice and contribute for national policies for these rare diseases.

## Novel Mechanisms of Lipodystrophy

Abhimanyu Garg, MD

Division of Nutrition and Metabolic Diseases, Department of Internal Medicine & Center for Human Nutrition, UT Southwestern Medical Center, Dallas, TX 75390, USA

The understanding of molecular genetic bases of various lipodystrophy syndromes began in earnest around year 2000. Around that time, linkage analysis followed by positional cloning led to identification of mutations in *LMNA* for autosomal dominant, familial partial lipodystrophy; and in *AGPAT2* and *BSCL2* for the two major subtypes of autosomal recessive, congenital generalized lipodystrophy (CGL). Since then, many more genes have been implicated in other subtypes of lipodystrophies, including *CAV1*, and *CAVIN1* (*PTRF*) for CGL; *PPARG*, *AKT2*, *PLIN1*, and *ADRA2A*, for autosomal dominant FPL; *CIDEc*, *LIPe* for autosomal recessive FPL; and *ZMPSTE24*, *POLD1*, *PIK3R1*, *PSMB8*, *FBN1*, *POLR3A*, and others for ultra-rare syndromes. Despite this progress, some affected subjects with various subtypes of lipodystrophies, especially FPL lack mutations in these genes, suggesting additional loci. While some patients with FPL phenotype may have polygenic basis for their lipodystrophy, others have clear evidence of monogenic inheritance and these families will lead to identification of novel loci. Overall, these discoveries support the role of several pathways involved in adipocyte biology, such as triglyceride and phospholipid biosynthesis; adipocyte differentiation; maintenance of nuclear membrane integrity; genomic stability; lipid droplet and caveolae formation and triglyceride storage; lipolysis and immunoproteasome-mediated proteolysis. Based on this understanding, it is expected that the novel loci for lipodystrophy will play an important role in adipocyte biology and may lead to elucidation of other essential pathways.

## Metabolic Surgery for Lipodystrophy

*Audrey Melvin, MB, BCh, MRCPI*

Bariatric surgery has evolved from its early role as a weight management procedure to an effective therapy in the management of the metabolic complications of obesity. Despite the contrasting volume and distribution of adipose tissue, there is significant overlap between lipodystrophy and obesity in the type and severity of metabolic complications observed, specifically insulin resistance, altered glucose homeostasis, dyslipidaemia and NAFLD. We now understand that much of this overlap is accounted for by varying degrees of impaired adipose tissue expandability. Although the mechanisms by which metabolic surgery improve health outcomes is multifaceted, we know that at least in part it influences satiety through its stimulation of enteroendocrine peptides. In lipodystrophy where dietary interventions form the cornerstone of its management, but compliance is often challenging, metabolic surgery offers an alternative approach. In many countries however, a threshold for body mass index must routinely be met before patients qualify for metabolic surgical interventions. To this end, we have detailed the metabolic response of patients with familial partial lipodystrophy 1(FPLD1) who have undergone Roux-en-Y gastric bypass surgery and discuss its future role in the management of individuals with partial lipodystrophy.

## **Objective Disease Criteria: Is This an Attainable Goal and What Do We Have to Do?**

### **Data from Michigan and NIH**

*Rasimcan Meral, MD<sup>1</sup>, Noemi Malandrino, MD PhD<sup>2</sup>, Rebecca J. Brown, MD<sup>2</sup>, Elif A. Oral, MD<sup>1</sup>*

1. Brehm Center for Diabetes Research and Division of Metabolism, Endocrinology & Diabetes, University of Michigan, Ann Arbor, Michigan
2. National Institute of Diabetes and Digestive Kidney Diseases, National Institutes of Health, Bethesda, Maryland

The diagnosis of lipodystrophy is a clinical one and depends largely on the clinical acumen of the physician. Establishing robust objective criteria needs to be prioritized. Dual Energy X-Ray Absorptiometry (DXA) technology has been of interest to lipodystrophy researchers with its unique capability of being able to quantify fat throughout the body. We have been acquiring total body composition scans in all our studies as an exploratory endpoint to study the change in %fat. Over the past 2 years, we had an interest in analyzing our collection DXA scans retrospectively to find a good diagnostic rule. Initially, we found a Fat Mass Ratio (Trunk %fat/Legs %fat) to be a somewhat useful parameter in females, but there was too much overlap with patients who had type II diabetes and non-alcoholic fatty liver disease. Later, we attempted to make use of the abundance of parameters produced by DXA by fitting a machine learning model. This approach yielded a well performing model as we found in an external validation study in collaboration with the NIH, but the sample size was only sufficient to produce a model for females. Finally, we managed to visualize fat from the DXA scans themselves by using a built-in color coding feature of the stock DXA analysis software (GE Lunar's enCore v14.10, Chicago, IL) as a band-pass filter for fat, which we termed as the "fat shadow". Investigators were able to identify the categories correctly when presented with a mixed set of lipodystrophy patients and controls in a completely blinded fashion that included males. We now propose the fat shadow as a tool to support and document the diagnosis of lipodystrophy in clinical and research settings. Future implications include remote expert opinion sharing and automated image processing for population screening in routine DXA's.

## **Lipodystrophy: The Impact of Metabolic Abnormalities**

*Carla Musso, MD*

Lipodystrophy syndromes are rare heterogeneous disorders characterized by deficiency of adipose tissue, usually a decrease in leptin levels and, frequently, severe metabolic abnormalities including diabetes mellitus, dyslipidemia and hepatic steatosis.

The pathogenesis of lipodystrophy is the irreversible widespread deficiency or dysfunction of adipose tissue. Regardless of the origin of lipodystrophy, the combination of adipose tissue loss and accompanying leptin deficiency is noted with ectopic fat deposition in the liver and muscle. This leads to insulin resistance, diabetes mellitus, and hypertriglyceridemia, which are often refractory to treatment with conventional lipid-lowering and glucose-lowering agents, as these metabolic abnormalities are typically more severe than those associated with obesity and type 2 diabetes.

To treat or prevent these severe complications of lipodystrophy requires aggressive treatment and management over the lifetime of the patient. Improvement in glycemic control is important to reduce the acute negative impact of hyperglycemia and the long-term impact of microvascular complications of diabetes. Reduction of triglyceride levels is critical since elevated levels increase the risk of acute pancreatitis and cardiovascular disease. Affected patients develop a hypertrophic “lipotoxic” cardiomyopathy, with both diastolic and systolic dysfunction, and have a predilection for cardiac dysrhythmias and early sudden cardiac death.

As ectopic fat accumulation and insulin resistance are driven by the inability to store excess calories in adipocytes, one effective therapeutic approach is to reduce caloric intake; however, this is often nearly impossible in patients with GL who have very low leptin levels, causing hyperphagia.

The knowledge of the disease and its dangerous consequences forced us to get to target to avoid macro and microvascular complications.

## Beyond Leptin: New Clinical Trials on the Horizon for Familial Partial Lipodystrophy

*Elif A. Oral, MD, MS*

Nevin Ajluni, Rasimcan Meral, Baris Akinci, Diana Rus, Rita Hench, Adam Neidert and Andra Stratton with Lipodystrophy United

Familial Partial Lipodystrophy is a cluster of heterogeneous diseases characterized by selective absence of adipose tissue from the peripheral depots with ectopic deposition, leading to severe insulin resistance and dyslipidemia. The conditions lead to multi-systemic involvement and progress to ischemic heart disease, heart failure, liver and kidney failure and ultimately early mortality. Metreleptin, a recombinant form of adipocyte hormone leptin has been in clinical development for these conditions since 2000, but while the FDA approved this drug for generalized lipodystrophy, it was not approved for FPLD in the US. There is an unmet medical need for the treatment of these conditions. This talk will focus on the issues leading to the problems of approval in the US, and ways to potentially address these concerns. The biggest obstacle in getting a novel treatment approved for these conditions is the heterogeneity and lack of precise diagnostic criteria. We have recently undertaken certain strategies to define these syndromes more precisely using morphomic criteria. In addition, we will review novel treatment strategies currently under development around the globe. These include but are not limited to anti-sense inhibitors of apoC3 and ANGPTL-3.

## Role for Next Gen Sequencing in Clinical Medicine

*Toni Pollin, Ms, PhD, CGC*

Recent decades have seen great strides in the ability to identify genetic causes for disease and enable individualized treatment, genetic counseling, and family testing. Prior to the sequencing of the human genome, patients with disorders suspected to be caused by a mutation in a single gene underwent either mutation panel testing or sequencing for that gene, or sequentially if there were multiple possible genes. While sequencing single genes continues to be standard for diseases such as cystic fibrosis with one known causal gene, the advent of next-generation sequencing, with its dramatically decreased cost and higher throughput, has made it possible to sequence multiple genes and even entire exomes and genomes on a clinical basis. We are completing an genomic medicine implementation project, "The Personalized Diabetes Medicine Program," funded by NIH as part of the IGNITE (Implementing Genomics in Practice) Network, to implement, disseminate and evaluate a sustainable approach to identifying, genetically diagnosing and promoting individualized treatment for individuals with monogenic forms of diabetes. Our approach includes screening/referral, next generation sequencing of 40 genes, classification, results disclosure and genetic counseling and testing of family members. To date, of 269 individuals with suspected monogenic diabetes sequenced, 26 individuals (9.7%) with 24 pathogenic or likely pathogenic disease variants in six genes have been identified, including two individuals with LMNA mutations not previously picked up as having familial partial lipodystrophy, enabling access to more individualized care and genetic counseling recommendations based on their molecular diagnosis.

## Laminopathies: A Personal, Basic Science Perspective

*Sonia Rehal, MSc, PhD*

Mutations in nuclear lamina genes give rise to a group of hereditary diseases known as laminopathies. Laminopathies lead to a wide spectrum of diseases, including Hutchinson Gilford progeria, familial partial lipodystrophy and type 2 Charcot--Marie--Tooth disease. Though the genetic information is within our reach, the genotype--phenotype connection is unclear. Specifically, the mechanisms by which laminopathies can cause tissue--specific pathology, when they are ubiquitously expressed) are largely unknown.

To resolve this paradox, the mechanisms by which nuclear lamins regulate transcriptional activity within the cell need to be addressed. From earlier studies in *xenopus* oocytes to elegant studies in cells from patients with Hutchinson Gilford progeria, we have possible clues as to how mutations in nuclear lamins can alter nuclear stability at the levels of gross morphology and chromatin dynamics.

From the perspective of a patient directly affected by familial partial lipodystrophy caused by a LMNA mutation, I will attempt to offer a brief description of the function of the nuclear lamins and laminopathies. Moreover, as a patient who experiences multiple organ dysfunction in this disease, I will try to unravel possible mechanisms by which they cause organ--specific disease.

Finally, the global significance of laminopathy research will also be addressed with the context of more common diseases such as obesity and metabolic syndrome.

## Mechanisms Underlying Lipodystrophy and Potential Therapies: A View from the Lab

*Justin Rochford, BSc, PhD*

The study of genes causing syndromes of lipodystrophy can reveal potential novel therapeutic avenues for the treatment of these rare diseases and also fundamental insights regarding adipose tissue development and function. Disruption of the gene *BSCL2*, encoding the protein seipin, causes severe generalised lipodystrophy. We have sought understand the molecular mechanisms via which the loss of seipin causes a near complete lack of adipose tissue. We have also studied *in vivo* models of seipin disruption, which have revealed new insights regarding the physiological effects of seipin loss. This work has also uncovered new information about the development of different adipose depots and their influence on metabolic health.

## Mechanisms of Insulin Resistance in Lipodystrophy and a Potential New Therapeutic Approach

*Gerald I. Shulman, MD, PhD*

Nonalcoholic fatty liver disease (NAFLD) is a major factor in the pathogenesis of type 2 diabetes (T2D) and nonalcoholic steatohepatitis (NASH). This presentation will focus on the cellular mechanisms of liver and muscle insulin resistance in humans and the role of dysregulated intracellular lipid metabolism in its pathogenesis. Specifically this talk will review recent studies that have implicated increases in ectopic lipid content in causing insulin resistance in these organs as well as recent studies that have implicated diacylglycerol, as the molecular trigger for lipid-induced insulin resistance through its activation of PKC-epsilon in liver and PKC-theta in skeletal muscle leading to inhibition of insulin signaling and the identification of Thr<sup>1160</sup> phosphorylation on the insulin receptor as a mediator of lipid-induced hepatic insulin resistance. This talk will also review recent studies that identify the link between white adipose tissue inflammation and increased rates of hepatic gluconeogenesis and fasting hyperglycemia in patients with type 2 diabetes due to increased rates of lipolysis leading to increased hepatic acetyl CoA content and allosteric activation of pyruvate carboxylase. Finally, I will discuss our recent studies demonstrating the potential utility of promoting liver-targeted hepatic mitochondrial inefficiency as a novel therapeutic approach to treat NAFLD, NASH and type 2 diabetes associated with lipodystrophy.

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## Inherited and Acquired Lipodystrophies: Clinical, Metabolic and Molecular Genetic Characteristics in Russian Population

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**Background:** Lipodystrophy syndromes form a group of heterogeneous rare disorders characterized by selective loss of body fat, which can be generalized (GL) or partial (PL), inherited or acquired. Lipodystrophy can also be a sign of progeroid syndromes (PS). Genetic diagnostics may be challenging because of many candidate genes and similar phenotypes. There is a lack of information on clinical and molecular-genetic characteristics of lipodystrophy syndromes in Russian population and the condition is usually misdiagnosed.

**Objective:** to assess the clinical and molecular-genetic characteristics of lipodystrophies in Russian population.

**Materials and methods:** 58 patients (45 adults and 13 children) from 51 families with different lipodystrophic fat loss patterns were included in the study: 40 patients (69%) with PL, 12 patients (20,7%) with GL, and 6 patients (10,3%) with PS. Detailed clinical examination and the assessment of metabolic abnormalities was performed. Leptin, insulin and C-peptide levels were measured in patients plasma, HOMA-IR index was calculated. Hyperinsulinemic euglycemic clamp-test was performed in 14 patients. Total body fat was assessed by DEXA. For genetic confirmation of the diagnosis 18 congenital lipodystrophies, insulin resistance and progeroid syndromes with lipodystrophies candidate genes (AGPAT2, BSCL2, CAV1, PTRF, PSMB8, LMNA, PPARG, PLIN1, AKT2, CIDEC, LIPE, LMNB2, POLD1, PIK3CA, WRN, PPP1R3A, ZMPSTE24, BANF1) were sequenced using a Custom Ion Ampliseq panel and PGM semiconductor sequencer (Ion Torrent).

**Results:** Mean age of the GL patients was  $20,17 \pm 14,78$  years, comparing to  $36,07 \pm 16,13$  years in the PL group ( $p=0,005$ ). The median age of the diagnosis of lipodystrophy also differed significantly in those 2 groups: 2,5 [1; 14,8] years for GL comparing to 15,5 [8,5; 29,5] for PL ( $p=0,005$ ). 87,5% of PL patients were female, comparing to the 58% in GL and 33% in PS. In the GL group 66,7% of patients had diabetes, 8,3% had pre-diabetes, in the PL group 57,5% of patients had diabetes, 25% had pre-diabetes, and in PS patients 50% had diabetes, 16,7% had pre-diabetes. Patients with PL demonstrated significantly higher insulin resistance than patients with GL (HOMA-IR index for GL 1,36 [0,72; 6,22], for PL 8,0 [3,7; 18,86],  $p=0,024$ ). M-index correlated negatively with basal insulin levels and HOMA-IR index. Among diabetic patients, polyneuropathy was found in 40% of GL, 43,5% of PL and 66,7% of PS, proteinuria was registered in 40% of GL. Predictably, patients with GL had significantly lower leptin levels 0,95 [0,58; 2,0] ng/ml than patients with PL 5,2 [1,93; 11,4] ng/ml ( $p=0,004$ ). Leptin levels correlated positively with the amount of total body fat ( $r = 0,657$ ;  $p=$

0,002). As many as 41,7% of the GL patients had associated autoimmune disorders. At the same time in 75% of GL patients no mutations in candidate genes were found, there were 2 patients with homozygous mutations in AGPAT2 and BSCL2, and 1 with heterozygous mutation in PPP1R3A. In 52,5% of PL patients mutations in the following genes were found: 4 in LMNA, 1 in PPARG, 1 in AKT2, 1 in LMNB2, 1 in PTRF, 1 in POLD1, 1 in PPP1R3A. The most common mutation was a heterozygous R482W mutation in the 8 exon (hot-spot) of the LMNA gene found in 4 families (7 patients) with PL. In PS group there were 3 patients (50%) with Werner syndrome in whom WRN mutations were found, 1 atypical progeria due to LMNA mutation.

Conclusion: Lipodystrophy syndromes in Russian population are very heterogeneous and can affect both children and adults. We recommend suspecting the possibility of a lipodystrophy syndrome in young patients with multiple metabolic disorders and the decrease of subcutaneous fat tissue. In case of clinical suspicion of FPL the search for the genetic cause should start from the 8 exon of LMNA. In other cases candidate genes panel is an effective diagnostic tool for differential diagnostics and confirmation of the diagnosis of the different forms of inherited lipodystrophies. When lipodystrophy is associated with autoimmune disorders it is less likely to find a mutation in a candidate gene.

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## Living with Lipodystrophy

*Andra Stratton, MA*

Panel Discussion Summary: A panel of patients and caregivers will share their stories of the impact of living with lipodystrophy. This discussion will highlight the physical and psycho-social impact the disease has on the affected person and the entire family. These important insights may help determine meaningful endpoints future research and clinical trials.

## **Novel Therapies to Address Unmet Medical Need for Patients with Lipodystrophy**

*Simeon I. Taylor, MD, PhD*

Despite availability of multiple drugs to treat diabetes and dyslipidemia, these drugs do not provide satisfactory solutions to address medical needs of patients with lipodystrophy. It was, therefore, it was a giant step forward when the FDA approved metreleptin as a therapy for patients with generalized lipodystrophy in 2014. On May 31, 2018, the European Medicines Agency's Committee for Medicinal Products recommended granting of marketing authorization for metreleptin as a treatment for both generalized and partial lipodystrophy. The success at gaining approval for metreleptin resulted from sustained collaboration among patients, academia, government, and industry. According to Novelion's website, annualized sales for metreleptin amount to ~\$75 million with ~70% of sales accounted for by prescriptions in the US. While metreleptin provides dramatic clinical benefit for many patients with generalized lipodystrophy, it does not provide a total cure. Furthermore, metreleptin delivers only limited efficacy in patients with partial lipodystrophy. Many obstacles complicate the challenges in addressing the remaining unmet medical need and advancing the standard of care: (1) scientific challenges to identify novel drug targets to guide development of innovative therapies; (2) financial challenges to fund repurposing of drugs targeting other therapeutic indications (whether approved or unapproved); (3) business challenges to fund R&D to develop new chemical entities to treat lipodystrophy; (4) regulatory challenges to define therapeutic indications to support development of Orphan Drugs; (5) reimbursement challenges to identify patients for whom payers will be willing to reimburse prices required to sustain drugs for very rare diagnoses.

## Cardio-Metabolic Assessment of Lamin A/C Gene Mutation Carriers: A Phenotype-Genotype Correlation

*Marie-Christine Vantyghem, MD, PhD*

AIMS: Mutations of the *LMNA* gene encoding lamin A/C induce heterogeneous phenotypes ranging from cardiopathies and myopathies to lipodystrophies. The aim of this study was to compare the cardio-metabolic complications of patients with heterozygous *LMNA* mutations at the 482nd codon, the hotspot for partial lipodystrophy, and carriers of other *LMNA* mutations.

METHODS and RESULTS: This study included 29 patients with R482 *LMNA* mutations and 29 carriers of another *LMNA* mutation (non-R482 group) from a university hospital, who were followed for a median of five years. The cardiac and metabolic phenotypes were compared between groups. A family history of cardiac implantable electrical device (CIED) ( $p<0.001$ ) or sudden death ( $p<0.01$ ) was more frequent in non-R482 than R482 carriers. The non-R482 carriers showed more electrocardiographic abnormalities and received CIEDs more often than R482 carriers ( $p<0.001$ ). On cardiac ultrasound, non-R482 patients had a higher frequency of left atrial enlargement ( $p<0.05$ ) and lower left ventricular ejection fraction ( $p<0.01$ ) than R482 carriers. In contrast, R482 carriers had lower BMI ( $p<0.05$ ), leptin ( $p<0.01$ ) and fat mass ( $p<0.001$ ), and a higher intra/total abdominal fat ratio ( $p<0.001$ ), and prevalence of diabetes ( $p<0.01$ ) and hypertriglyceridemia ( $p<0.05$ ) than non-R482 carriers, with a trend towards more coronary artery disease.

CONCLUSION: Non-R482 carriers presented with arrhythmias more frequently than R482 carriers, who were twice as often diabetic, suggesting that follow-up for laminopathies could be adjusted to the genotype. Non-R482 mutations require ultra-specialized cardiac follow-up. Coronary artery disease should not be overlooked. Although overlapping phenotypes exist, *LMNA* mutations essentially lead to tissue-specific diseases, favoring genotype-specific pathophysiological mechanisms.

## MFN2-related Multiple Symmetric Lipomatosis: Crossroads Between White and Brown Fat

Corinne Vigouroux, MD, PhD

Emilie Capel, Camille Vatier, Pascale Cervera, Tanya Stojkovic, Corinne Vigouroux and Isabelle Jéru

Multiple symmetric lipomatosis (MSL) is characterized by upper-body lipomatous masses frequently associated with metabolic and neurological signs. MFN2 mutations were recently implicated in a very rare autosomal recessive form of MSL. MFN2 encodes mitofusin-2, a mitochondrial fusion protein previously involved in Charcot-Marie-Tooth neuropathy (CMT). We performed clinical and metabolic investigations in six patients from five families carrying a MFN2 homozygous p.Arg707Trp pathogenic variant. Lipomatous tissues was studied in three patients.

Patients presented both lipomatous masses and a lipodystrophic syndrome (lipoatrophy, low leptinemia and adiponectinemia, hypertriglyceridemia, insulin resistance and/or diabetes). CMT was of highly variable clinical severity. Lipomatous tissue contained hyperplastic unilocular adipocytes with few multilocular cells and displayed numerous mitochondrial alterations (increased number and size, structural defects). As compared to subcutaneous fat from controls, mRNA and protein expression of leptin and adiponectin was strikingly decreased while the CITED1 and FGF21 thermogenic markers were strongly overexpressed. FGF21 serum level, measured in 5 patients, was markedly increased, and 18F-FDG-PET-scan, performed in 4 patients, revealed increased fat metabolic activity. MFN2-related MSL is a novel mitochondrial lipodystrophic syndrome with adipose tissue dysfunction involving both lipomatous masses and lipoatrophy. Its complex neurological and metabolic phenotype justifies careful clinical evaluation and multidisciplinary care. Low leptinemia and adiponectinemia, high serum FGF21 and increased 18F-FDG body fat uptake may be disease markers.

# POSTER PRESENTATIONS

## A Retrospective Review of Antidepressant use in Patients with Lipodystrophy Attending the Severe Insulin Resistance Service

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Lipodystrophy refers to a group of rare conditions characterised by a generalised or partial lack of body fat and is associated with severe metabolic problems e.g. severe insulin resistance, diabetes, non-alcoholic fatty liver disease and pancreatitis. In addition to its metabolic effect, lack of adipose tissue also has a significant impact on physical appearance which many patients find very distressing. It has been highlighted by people living with lipodystrophy that the psychological effects of lipodystrophy can be as challenging as the metabolic consequences. However, there is little information about the prevalence of mental health disorders in this patient group.

**Aim:** To identify how many people with lipodystrophy attending the Severe Insulin Resistance (SIR) Service are on antidepressants and/or have a documented mental health condition.

**Methods:** A retrospective review of clinical notes was conducted on all patients with lipodystrophy who have attended the SIR Service since its inception in 2011 (n=170).

**Results:** The clinic medical records suggested that 40% (68/170) of patients were on antidepressants and 11% (21/170) had 1 or more mental health diagnoses (depression n=9, anxiety n=4, bipolar n=3, schizoaffective disorder n=1, obsessive compulsive disorder n=3, borderline personality disorder n=1, body dysmorphism n=1).

**Conclusion and Implications for practice:** There is a very high use of antidepressants in patients with lipodystrophy attending the SIR clinic. This compares to between 10-20% in the General Type 2 Diabetes Setting (Mast et al 2017, Wang et al 2016). Although some patients have a documented mental health diagnosis, this may not be a true reflection of all diagnoses as we rely on patients to report this to us.

**Future plans:** Further research is needed to establish the prevalence of depression and anxiety and other common mental health conditions for people living with lipodystrophy. This information can then be used to develop and test a psychological support intervention.

## Burden of Illness Associated with Generalized Lipodystrophy in Leptin Replacement Therapy-Naïve Patients: A Longitudinal Medical Chart Review Study

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**Introduction:** Generalized lipodystrophy (GL) is an ultra-rare disorder characterized by lack of adipose tissue, hyperphagia, and altered physical appearance. GL is associated with increased risk of organ abnormalities and potentially accelerated death. Complications of GL have been reported in small-scale studies, but understanding of GL's disease burden is limited.

**Methods:** This study is the largest assessing the burden of illness associated with GL using longitudinal, retrospective, multi-center medical chart review data. Medical records of patients (pts) with confirmed non-HIV-related GL, never treated with leptin replacement therapy, from the National Institutes of Health, the University of Michigan, and Dokuz Eylul University, in Turkey, were reviewed. Pts were observed from birth to loss to follow-up, death, or end of chart abstraction. Date of first symptoms was defined as the onset of GL-related signs/symptoms (e.g., diabetes, elevated ALT). Physical characteristics were assessed at last visit. Lifetime prevalence of organ abnormalities of the liver, pancreas (including diabetes), kidney, and heart was determined. Kaplan-Meier curves were used to describe 1) time to first organ abnormality from the date of first symptoms, 2) time to progression (2<sup>nd</sup> organ abnormality) from first organ abnormality and 3) time to death from birth. A time-varying Cox model was used to describe the association between number of organs with abnormalities and death. Hazard ratio (HR) and 95% confidence interval (CI) are reported.

**Results:** Among 56 eligible pts, 58.9% were female. Pts experienced first symptoms at mean age 11.5 years; diagnosis of GL occurred 3.9 years later at age 15.4 y (SD=14.4). Most pts (87.5%) had congenital GL, 8.9% had acquired GL and 3.6% had generalized progeroid lipodystrophy. The five physical characteristics most often observed were muscular appearance, hepatomegaly, lack of facial fat, prominent veins and acanthosis nigricans. Lifetime prevalence of organ abnormalities was 89.3% for liver, 67.9% for pancreas (53.6% diabetes, 12.5% pancreatitis), 50.0% for kidney, and 39.3% for heart. 92.9% of pts had ≥1 organ with abnormalities after appearance of first symptoms, with a median (IQR) time to first organ abnormality of 5.0 (0.8-12.7) years. 53.8% had a second organ abnormality a median (IQR) of 5.7 (2.0-10.4) years later. Among the 14.3% of pts who died, median (IQR) age at death was 31.7 (29.3-48.4) years. A positive association existed between number of organs with abnormalities and death (HR=3.8, 95%CI= 2.2-6.6, p<.0001).

**Conclusions:** This large study documents the high burden of GL and is the first to quantify the high risk of organ abnormalities, survival/mortality patterns, and the association between organ abnormalities and death. Since more severe patients may have sought leptin therapy under ongoing research studies, evaluation of leptin-naïve patients may underestimate the impact of GL on all patients.

## **Effect of Leptin Replacement Therapy on Survival and Disease Progression in Generalized and Partial Lipodystrophy (GL, PL)**

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**Aim:** This study uses data on patients treated with leptin therapy (LT) and matched untreated patients to estimate the average treatment effect (ATT) of LT via metreleptin on disease progression and mortality.

**Methods:** Data on 103 treated patients were obtained from a clinical trial of leptin therapy, documented in the LT Follow-Up study. The GL/PL Natural History study is a retrospective, non-interventional, observational, closed cohort, longitudinal study assessing the clinical and demographic characteristics of 230 patients with GL and PL. The matching technique pairs each treated patient with an untreated patient in the GL/PL Natural History study whose history of symptoms at the index observation date matches that treated patient's symptoms at trial enrollment. The analysis focuses on four abnormalities related to the heart, kidneys, liver, and elevated levels of HbA1c. Developing a 2nd, 3rd, or 4th abnormality is considered a progression event. A Cox proportional hazards model was used to estimate the difference in mortality risk between the two patient groups.

**Results:** LT is associated with a 53.7% decrease in the risk of progression from two abnormalities to three abnormalities, a 55.7% decrease in the risk of progression from three abnormalities to four abnormalities, but no significant effect on progression from one to two abnormalities, likely due to limited observation of treated patients with only one abnormality. LT is associated with a 71.9% decrease in mortality risk. Kaplan-Meier survival curves for treated and untreated cohorts confirm this result. Sensitivity analyses, including methodological sensitivities, adjustments to the study sample, and how clinical markers are treated, shows robustness of results.

**Conclusions:** LT was found to be associated with a statistically significant reduction in the risk of progression from 2 to 3 abnormalities, and from 3 to 4 abnormalities, on the order of 50%. LT was also found to be associated with a statistically significant reduction in the risk of mortality on the order of 70%. These results are robust to a wide range of changes to the baseline specification.

## **Efficacy of Recombinant Human Leptin (Metreleptin) in Nonalcoholic Steatohepatitis (NASH) Associated with Partial Lipodystrophy**

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**Aim:** We aimed to characterize the effects of metreleptin therapy on the liver disease associated with partial lipodystrophy (PL) in a diverse group of patients.

**Methods:** Twenty-three patients with PL associated fatty liver disease were enrolled in this an open-label study (ClinicalTrials.gov identifier: NCT01679197). Patients were treated with metreleptin for 12 months. One patient was excluded as no NASH was detected on baseline liver biopsy. Nineteen patients completed 1 year of metreleptin treatment and 18 completed a second liver biopsy. To evaluate hepatic fat content, magnetic resonance (MR) imaging using quantitative multi-echo Dixon method and multi-echo MR-spectroscopy was utilized. Total NASH scores and NAFLD activity scores (NAS) were calculated from transcutaneous liver biopsy specimens.

**Results:** A significant decrease in fasting triglyceride, liver enzymes (ALT and AST) and resting energy expenditure (REE) were observed 12 months after metreleptin. Fasting glucose and HbA1c levels also tended to be decreased after treatment but the effect was not statistically significant. NASH scores showed a decrease from  $6 \pm 2$  to  $5 \pm 2$  ( $p = 0.0079$ ). NAS scores also decreased from  $5 \pm 1$  to  $4 \pm 1$  ( $p = 0.0002$ ). Liver fat, quantified by MR Dixon method, decreased from baseline, mean  $13.3 \pm 6.6\%$  to  $8.4 \pm 5.2\%$  after 12 months of metreleptin ( $p = 0.0014$ ). Responders (with a NASH score decrease of 2 points or more from baseline, without an increase in fibrosis) had a significantly higher basal carbohydrate intake. Baseline leptin level did not meet statistical significance but did tend to be lower in the responder group.

**Conclusion:** Metreleptin therapy has a favorable effect on PL associated NASH, particularly on steatosis. Lower leptin level tends to predict response; however, setting this cut-off too low may miss patients who would benefit from treatment. Future collaborative efforts with other investigators would allow the potential to combine data sets and determine predictive levels of response.

## **Role of Telomere Lengthening in Type 2 Partial Lipodystrophy**

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**Introduction:** Lipodystrophies are a group of diseases characterized by loss of body fat. Among the genetic forms, the most prevalent is the autosomal dominant Familial Partial Lipodystrophy Type 2 (FPLD2), also called Dunnigan's variant or Dunnigan's syndrome, characterized by a mutation specifically involving lamin A and C or LMNA gene. Commonly, the mutation causing FPLD2 involves the codon R482W, and to a lesser extent, the codon R644C (1). Evidence suggests that altering these proteins weakens the integrity and structure of the nuclear envelope, which would impair the structure of the adipocyte nucleus, ultimately leading to premature cell death. In addition, lamin A and C have been shown to bind to telomeric sequences (2,3). In this context, the objective of the present study is to investigate telomere size and to evaluate the relationship between telomeres and lamin A and C in individuals with Familial Partial Lipodystrophy type 2.

**Methods:** The study was carried out in the Diabetes Mellitus laboratory of the Clinical Hospital of Ribeirão Preto (HC-RP), with patients with FPLD selected in the Diabetes Outpatient Clinic of this same hospital and healthy individuals voluntarily recruited as controls. The study was approved by the Research Ethics Committee of the HC-RP (No. 2.501.481 / 2017). Biochemical analyzes of serum lipoproteins and glycemia were performed. Genomic DNA was extracted from the peripheral blood to assess, by the technique of Southern Blotting, the telomere length.

**Results:** There was no significant difference between the age groups of the control patients ( $37.25 \pm 5.40$ ) and those with the R644C ( $46.40 \pm 1.2$ ) and R482W ( $40.20 \pm 6.59$ ) mutations. However, we noticed a significant difference between the Body Mass Index (BMI) of the patients with the R644C mutation ( $28.28 \pm 1.30$ ) and the R482W mutation ( $22.94 \pm 0.91$ ,  $P < 0.05$ ), as well as between the triglyceride levels of the patients of the R482W mutation ( $271.8 \pm 66.47$ ,  $P < 0.05$ ) in relation to the control group ( $98.0 \pm 26.73$ ). There was a significant decrease in telomere length among the FPLD2 patients compared to controls and the R482W mutation showed a more pronounced reduction

**Discussion:** Preliminary results demonstrate that the R482W mutation probably determines a more aggressive disease profile, due to the greater loss of body fat and the alteration of biochemical and metabolic parameters.

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## The Use of Anthropometry to Evaluate Cardiovascular Risk in HIV Patients

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**Objectives:** To evaluate anthropometric measures/indexes and to propose cutoffs to identify cardiovascular risk in HIV-infected patients on highly active antiretroviral therapy (HAART).

**Methods:** We measured circumferences (waist, hip, neck and trunk) and calculated anthropometric indexes (body mass index, waist to hip ratio). To identify cardiovascular risk/events, we conducted exams of electrocardiogram; stress electrocardiography; ankle brachial index test; pressure arterial hypertension, lipid biochemical tests and blood glucose. To evaluate the performance of all anthropometric measures/indexes to predict cardiovascular risk we used ROC curves; and measures/ indexes that show better performance (area under the curve) were used to propose cutoff points (which had better combinations of sensitivity/specificity).

**Results:** Waist circumference (WC) showed the best performance to predict cardiovascular risk (Area under the curve: 0.83 and 0.86 for male and female, respectively), followed by neck circumference (NC) (AUC: 0.79 and 0.84 for male and female, respectively). All anthropometric measures/indexes presented different cutoff points from those proposed for the HIV seronegative population. The cutoff points for WC were 87.75 cm (sensitivity: 82.2% and specificity 75.5%) for males and 90.5 cm (sensitivity: 84.0% and specificity 73.0%) for females.

**Conclusions:** The measure of central adiposity (WC) presented better performance than the total adiposity index (BMI) in evaluating cardiovascular risk. Anthropometry is cheap and convenient, cheap and reliable tool that can be used in clinical practice routinely, allowing early interventions.

## **Metreleptin Effects on Mixed Meal Response in Partial Lipodystrophy**

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Partial lipodystrophy (PL) is associated with diabetes, dyslipidemia and steatohepatitis with variable fat loss. Post-meal fuel kinetics or incretin responses are not carefully studied in PL and effects of metreleptin (ML) on these are not known. In order to investigate these questions, 14 patients (3M/11F, ages 12-64 yrs) with PL were studied (HbA1c: 8.7 ± 1.8%, body fat % 31.0 ± 9.8 and liver fat 12.4 ± 6.5%). Patients were treated with ML (Aegerion Pharmaceuticals, Cambridge MA) at a daily dose of 2.5-10 mg and underwent a mixed meal test (MMT; with 474 ml of Optifast; 320 kcal, 50% carbohydrates, 15% fat, 35% protein) before starting ML and at 1 yr. Blood samples for metabolic and hormonal measurements were collected at 0, 30, 60, 90, 120 and 180 minutes of the test. The improvement in glucose levels with ML was seen predominantly during post-meal time points. Insulin levels at fasting and post meal were comparable between baseline and post ML. Fasting and post meal FFA and triglyceride levels were significantly lowered with ML therapy. Neither the suppression of FFA nor the lack of a rise in triglycerides post MMT was affected by ML. The predominant post-meal incretin was GIP and the peak secretion was significantly lower after ML. In conclusion, metabolic effects of ML in PL include lowered post meal glucose, triglyceride and FFA levels and attenuated GIP secretion.

**Table: Metabolic and hormonal parameters during mixed meal test in PL**

Measurement (mean±SD)	Baseline	12-months	p-value
60 min Glucose peak (mg/dl)	273 ± 83	234 ± 77	0.0431
AUC Glucose (mg/dL x hr)	751 ± 268	603 ± 197	0.0302
Fasting Triglycerides (mg/dl)	577 ± 467	345 ± 238	0.0343
Fasting FFAs (mEq/ml)	0.54 ± 0.21	0.45 ± 0.19	0.0501
60 min GLP-1 level (pg/ml)	29.0 ± 40.0	19.9 ± 20.6	NS
60 min GIP level (pg/ml)	334.9 ± 156.0	208.7 ± 112.2	0.0046
GIP AUC (pg/ml x hr)	715.7 ± 325.9	567.5 ± 270.7	0.0408

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## ApoC-III Levels Correlate with HbA1c in Familial Partial Lipodystrophy: Observations from the Broaden Study

Meral R, Digenio A, Neidert AH, Tami J, and Oral EA on behalf of BROADEN STUDY INVESTIGATORS

Familial Partial Lipodystrophy (FPLD) is a heterogeneous and complex metabolic disease. The unifying feature is selective absence of subcutaneous adipose tissue from extremities and compensatory hypertrophy of residual depots. There is severe insulin resistance, steatohepatitis and severe dyslipidemia characterized by primarily hypertriglyceridemia. The syndromes are often, monogenic and sometimes polygenic, with the monogenic forms being more severe. ApoC-III is a 79 amino acid glycoprotein synthesized principally in the liver and plays a key role in determining serum triglyceride levels. It has been found to be a potent inhibitor of lipoprotein lipase and the hepatic uptake of Triglyceride-Rich Lipoproteins. Reducing Triglyceride levels in FPLD patients by inhibiting ApoC-III may reduce the risk of pancreatitis, improve insulin sensitivity and reduce liver fat. BROADEN study is the first randomized placebo-controlled study in the FPLD population. Here we evaluate the baseline characteristics of 40 FPLD patients (11M:29F, Age:  $47 \pm 11$  years) enrolled in the study. We aimed to investigate the relationship of the baseline ApoC3 levels to numerous metabolic, adiposity and ectopic fat related markers (liver MRI and Echo). ApoC3 levels are elevated in FPLD and correlate positively with triglyceride levels ( $R^2=0.49$ ,  $p<0.001$ ) as expected. Interestingly, we also noted a positive relationship with HbA1c in the patients presenting with  $HbA1c > 6.5\%$  ( $R^2=0.12$ ,  $p=0.05$ ). Enrollment with the set criteria has been challenging primarily due to the high triglyceride criteria and the exclusion of multiple comorbidities. We observed a high rate of splenomegaly and kidney function abnormalities in the recruited population which deserves further study.

## Diagnosis of Familial Partial Lipodystrophy Using Dexa Scans: Proof of Concept for Applying Machine Learning to Detect a Rare Disease

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Familial partial lipodystrophy (FPLD) is a rare heterogeneous disorder with selective absence of peripheral fat and increased upper body adiposity and ectopic fat depots. As there are drugs in development for this condition, objective diagnostic criteria for distinction from common truncal obesity and Type 2 diabetes is of importance. Our overarching goal is to develop objective, quantitative diagnostic disease criteria for FPLD that demonstrate and stage distinctive morphological characteristics as encountered in individuals displaying a spectrum of adiposity and metabolic abnormalities. Dual Energy X-ray Absorptiometry (DEXA) quantifies fat with sufficient spatial resolution that is possible to computationally characterize both its distribution and structural composition by use of convolutional neural network techniques in tandem with semi-supervised machine learning. Initial application of convolutional neural networks (CNNs) on DEXA digital imagery generated a candidate automated classifier that exhibited both high sensitivity and specificity, confirming the hypothesis that such imagery could benefit from computational interrogation. Baseline data from participants in various clinical studies [supported by NIH grants R01 DK088114, R21DK098776 (EAO) T32DK007245 (JH)] were analyzed retrospectively, and patients were matched according to sex, age and fat free mass index (FFMI). A Support Vector Machines (SVM) with radial kernel was used to develop a model using 6 regional fat parameters (arms, legs, trunk, android, gynoid and total tissue percent fat). Dimensionality reduction was applied using Principal Component Analysis (PCA). PC's 1 and 2 explained 94% of the total variance. Analyses were done using R (v3.3.3) and packages e1071 (v1.6.8) and pROC (v1.10.0). SVM was tuned to  $\gamma=0.066$  and  $c=15$ . 15 females with a clinical diagnosis of FPLD (Age:  $48\pm10$  years; BMI:  $27.2\pm5.7$  kg/m<sup>2</sup>; FFMI:  $18.7\pm2.1$  kg/m<sup>2</sup>) and 25 matched control females (Age:  $49\pm11$  years; BMI:  $34.0\pm5.2$  kg/m<sup>2</sup>; FFMI:  $18.8\pm2.2$  kg/m<sup>2</sup>, 15 with diabetes) were used as the training set. Cross-validation accuracy within training data was 97.5%. Testing was performed on a different data set consisting of 25 females with FPLD and 25 females without FPLD with the model correctly classifying 23 patients with FPLD and 24 patients without (sensitivity: 92%, specificity: 96%). ROC AUC was 0.96 (CI: 0.91-1.00). Additionally, the raw imagery data was processed by use initially of the Spatially Invariant Vector Quantization (SIVQ) algorithm, with subsequent application of Random Forest (RF) techniques (DataRobot application suite), yielding pilot ROC curves with AUC of 0.9808. We conclude that applying image analytic pipelines and machine learning techniques to DEXA body composition images, including PCA and SIVQ/RF, may prove useful in defining and detecting abnormal fat distribution.

## ECG and Echo Characteristics in Familial Partial Lipodystrophy: The Impact of Lamin A Variants

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Familial partial lipodystrophy (FPLD) is an inherited, rare syndrome characterized by selective absence of adipose tissue from extremities which is associated with severe insulin resistance, and metabolic dyslipidemia (with hypertriglyceridemia, and low HDL). Typically, 30-50 % of patients with FPLD demonstrate a pathogenic variant in Lamin A (LMNA) gene that is associated with inherited cardiomyopathy and arrhythmia syndromes. We inquired the prevalence of having abnormal ECGs and echocardiograms in FPLD and whether there is a difference in evaluated parameters with respect to genotype.

**Methods:** We conducted a retrospective review of an established cohort of 58 patients (age range: 12-71, M/F 8/50) with FPLD. Demographic characteristics, genotype, fasting triglyceride, hemoglobin A1c, LDL and HDL levels were collected; ECGs and echocardiograms were also interrogated.

**Results:** Out of 58 patients, 22 (38 %) displayed a pathogenic variant in the LMNA gene. Various characteristics are displayed in Table 1. Seventy-one % of patients (41/58) had an abnormal ECG and echocardiogram (Table 2). 40% (23/58) of the patients displayed an arrhythmia on the ECGs (13 in the patients with LMNA variants and 10 in the non LMNA group). The likelihood of having an arrhythmia was significantly higher in the patients with LMNA variants versus those without (odds ratio of 3.4, CI 1.1-10.6).

**Conclusions:** The overall prevalence of abnormal ECHO and/or ECG is high at 45/58 (78 %) in FPLD. Patients with LMNA variants have a 3.4 times increased risk of developing cardiac arrhythmias compared to those without. We recommend vigilant monitoring for cardiac disease in FPLD and for arrhythmias in patients with FPLD and LMNA variants.

**Table 1.** Clinical characteristics of patients with familial partial lipodystrophy

<i>mean (range)</i>	LMNA variants <i>n</i> = 22	Non-LMNA controls <i>n</i> = 36	<i>p</i> value <sup>a</sup>
<b>Mutation</b>			
LMNA p.R482Q	10	0	
LMNA, other	12	0	
Other or none identified	0	36	
<b>Demographics and Characteristics</b>			
Sex	19F:3M	31F:5M	.1
Age (years)	49 (12 – 71)	49 (16 – 70)	.99
Race, <i>n</i> (%)			
White	16 (73%)	31 (86%)	.44
Black	1 (4%)	1 (3%)	
Other or unknown	5 (23%)	4 (11%)	
Body weight (kg)	76.9 (51.9 – 114.3)	87.4 (49 – 119)	.08
Height (cm)	165.2 (155 – 176.3)	165.7 (150.4 – 187)	.93
BMI (Kg/m <sup>2</sup> )	28.1 (21.6 – 39)	31.6 (17.2 – 42.5)	.06
Hemoglobin (g/dl)	13.3 (10.0 – 15.6)	13.1 (8.7 – 15.7)	.59
Minimum Triglycerides (mg/dl)	252 (74 – 977)	228 (42 – 969)	.85
Maximum Triglycerides (mg/dl)	1063 (113 – 5503)	2074 (156 – 8889)	.07
Low density lipoproteins (mg/dl)	99.5 (35 – 177)	91.1 (23 – 184)	.48
High density lipoproteins (mg/dl)	42.5 (26 – 88)	36.5 (18 – 62)	.12
Minimum HbA1c (%)	6.5 (5.3 – 8.4)	7.3 (4.4 – 10.4)	.046
Maximum HbA1c (%)	7.8 (5.5 – 10.3)	9.9 (4.5 – 15.4)	<.01
Left ventricular ejection fraction (%)	59 (34 – 68)	62 (57 – 75)	.68

a. Chi-square/Fisher test and Wilcoxon Rank-Sum tests for categorical and continuous characteristics, respectively.

Table 2. Presence of cardiac disease in patients with familial partial lipodystrophy

Results	LMNA variants n=22	Non-LMNA controls n=36	p-value <sup>a</sup>
Arrhythmia n (%)	13 (59%)	10 (28%)	
Odds ratio (95% CI):			
Unadjusted	3.8 (1.2-11.5)		0.02
Adjusted for comorbidities	3.4 (1.1-10.6)		0.03
Left Ventricular Hypertrophy n (%)	7 (32%)	9 (25%)	
Odds ratio (95% CI):			
Unadjusted	1.4 (0.4 -4.5)		0.57
Cardiomyopathy n (%)	2 (9%)	1 (3%)	
Odds ratio (95% CI):			
Unadjusted	3.5 (0.3-41.1)		0.55
	Other LMNA variants n=12	LMNA p.R482Q n=10	
Arrhythmia n (%)	9 (75%)	4 (40%)	
Odds ratio (95% CI):			
Unadjusted	4.5 (0.7 – 27.7)		0.19 <sup>b</sup>

a. Chi-square was used for categorical characteristics, Fisher test was used when expected counts were less than 5

b. Fisher test was used

## **Clinical Predictors of Leptin Response for Improvement in Liver Histopathology in a Cohort of Patients with Partial Lipodystrophy**

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Partial lipodystrophy is a heterogeneous metabolic disorder characterized by selective absence of adipose tissue from the periphery with severe insulin resistance due to ectopic fat deposition especially in the liver. Metreleptin (ML, manufactured by Aegerion Pharmaceuticals, Cambridge, MA) has been shown to lead to metabolic improvement and amelioration of hepatic fat deposition as well as reduction in nonalcoholic steatohepatitis scores in some patients with partial lipodystrophy. Since not all patients with partial lipodystrophy respond uniformly, we have been interested in evaluating clinical predictors of leptin response. We have completed a clinical trial investigating the efficacy of ML in the liver in a cohort of patients with PL and previously reported results from an NIDDK sponsored clinical trial in which the primary endpoint was the reduction in total nonalcoholic steatohepatitis (NASH) scores. Out of 23 patients (22 with familial, one acquired, 78.3% female, aged 12-64 years) with PL and NAFLD who were recruited, 18 completed 1 full year of treatment and 9 completers had more than 2-point reduction in total NASH score after 12 months of therapy without an increase in fibrosis scores and thus met the definition of clinical response. We had selected baseline HbA1c, triglyceride, insulin, fasting FFA and glucose levels, total adiposity at baseline, hepatic fat percent by MRI at baseline, total energy intake, total carbohydrate, fat and protein intake, baseline resting energy expenditure, respiratory quotient and baseline leptin levels as potential predictors of response. At the completion of the trial, we ran ROC analyses on these baseline parameters to determine if any of these predicted a responder status for clinically meaningful histological improvement in the liver. Out of these preselected parameters, area under the curve (AUC) for the ROC curves for baseline carbohydrate intake was 0.83 (with CI 0.63 to 1.0) ranking the best predictor of response. The same value reached statistical significance for baseline FFA (0.79, CI 0.53-1), insulin (0.77, CI 0.50-1.0), and leptin (0.78, CI 0.55-1.0). Baseline triglyceride, HbA1c, or glucose concentrations did not predict amelioration of liver histopathology. Likewise, baseline adiposity and hepatic fat % by MRI were not discriminatory for prediction of clinical response. Interestingly and consistently, responders had a significantly higher carbohydrate intake compared to non-responders and only they had a reduction in carbohydrate intake during the trial which was an effect evident at 3 months and sustained throughout 12 months. The reduction in carbohydrate intake appeared specific among macronutrient consumption parameters. These results show that the liver disease seen in partial lipodystrophy in some patients may be driven by relative leptin deficiency which may be linked to increased consumption of carbohydrates.

## **Fat Shadows from Dual Energy X-Ray Absorptiometry for Documentation of Fat Distribution in Patients with Lipodystrophy**

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**Objective:** Lipodystrophy syndromes are a heterogeneous group of disorders causing atypical diabetes, associated with selective absence of fat. The reference standard for diagnosis currently is the clinical acumen of the physician. With niche therapies either approved or under investigation, development of objective diagnostic tools for these syndromes are urgently needed.

**Methods:** Here we describe a new method using the built-in features of the enCore software v14.10 to render out non-fat tissues from Dual Energy X-ray Absorptiometry (DXA) scans to derive a "fat shadow", which is a color-coded representation of fat tissue on the DXA image. First, we developed the method and subsequently, performed a two-center, blinded evaluation to determine the usefulness of fat shadows as a diagnostic tool for lipodystrophy syndromes.

**Results:** We evaluated fat-shadows from 16 (11F:5M) Generalized Lipodystrophy (GL), 57 (50F:7M) Familial Partial Lipodystrophy (FPLD), 2 Acquired Partial Lipodystrophy (1F:1M) and 126 (90F:36M) controls. The observed fat distributions were consistent with the clinical diagnosis. FPLD was differentiated from controls with 85% sensitivity and 96% specificity (95%CI: 72-93 and 91-99, respectively). GL was differentiated from non-obese controls with 100% sensitivity and specificity (95%CI: 79-100 and 92-100, respectively).

**Conclusions:** Fat-shadows provided sufficient qualitative information to infer clinical phenotype. We propose that these fat-shadows could be used for accurate documentation of fat distribution in lipodystrophy and support the diagnosis. Further, the selective tissue rendering, and visualization may become useful in other metabolic diseases.

## Comorbidities of Lipodystrophy and Multisystemic Involvement

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Lipodystrophy syndromes are heterogeneous group of disorders characterized by generalized or partial loss of fat depots. They are associated with a high number of comorbidities involving multiple systems. We hypothesized that patients with Familial Partial Lipodystrophy (FPLD) would have more comorbidities compared to controls with type 2 diabetes, obesity and fatty liver disease (T2DM). Medical history and physical exam data that were collected at the baseline of parallel studies were analyzed retrospectively. FPLD patients were matched to T2DM patients according to gender and age. Frequencies were compared using Fisher's exact test. Data from 19 FPLD patients (15F:4M, Age=48±11 years, BMI=28±6 Kg/m<sup>2</sup>) 19 T2DM patients (15F:4M, Age: 52±10 years, BMI= 35±5 Kg/m<sup>2</sup>) were analyzed. In the medical history, it was found that leg and muscle related complaints were more frequent in the FPLD group than in the T2DM group. Other significant elements in patient history were fatigue, anxiety, tremor, pancreatitis and loss of sensation. In physical exam findings, presence of an abnormal neck (12 FPLD vs 3 T2DM, p=0.007) and the absence of striae (1 FPLD vs 8 T2DM, p=0.019) was significant. In conclusion, lipodystrophy is a distinct phenotype associated with disease specific comorbidities.

History of:	FPLD	T2DM	P-value
Muscle pain	11 out of 19 (58%)	1 out of 19 (5%)	0.001
Pain in legs w/walking	8 out of 19 (42%)	0 out of 19 (0%)	0.003
Anxiety	11 out of 19 (58%)	2 out of 19 (11%)	0.005
Fatigue	17 out of 19 (89%)	9 out of 19 (47%)	0.013
Leg/ankle swelling	10 out of 19 (53%)	2 out of 19 (11%)	0.013
Muscle weakness	8 out of 19 (42%)	1 out of 19 (5%)	0.019
Myopathy	6 out of 19 (32%)	0 out of 19 (0%)	0.020
Pancreatitis	6 out of 19 (32%)	0 out of 19 (0%)	0.020
Dizziness	5 out of 19 (26%)	0 out of 19 (0%)	0.046
High triglycerides	19 out of 19 (100%)	14 out of 19 (74%)	0.046
Physical exam finding:			
Abnormal neck (hypertrophic)	12 out of 19 (37%)	3 out of 19 (84%)	0.007
Striae are present	1 out of 19 (5%)	8 out of 19 (42%)	0.019

## Insulin Resistance, Cardiovascular Autonomic Neuropathy and Left Ventricular Hypertrophy in Patients with Congenital Generalized Lipodystrophy

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Congenital generalized lipodystrophy (CGL) subjects have a high prevalence of cardiovascular autonomic neuropathy (CAN) and cardiac complications, including left ventricular hypertrophy (LVH). This study aimed to analyze insulin resistance (IR), CAN severity and LVH association. A cross sectional study with 10 CGL patients and 20 healthy controls. We evaluated clinical and laboratory data, echocardiogram parameters, 3 spectral analysis components - high frequency (HF), low frequency (LF), and very low frequency (VLF) - of heart rate variability (HRV), sympathetic-vagal balance, time domains of HRV, corrected QT interval (cQT), and 4 cardiovascular reflexes tests (postural hypotension test, orthostatic, respiratory, and valsalva coefficients - 2 abnormal tests: clinic CAN, 1 abnormal test: incipient CAN, and postural hypotension: advanced CAN). In CGL group 50% had CAN (40% clinic and 10% incipient) and 40% LVH. There was inverse correlation between LVMI and HF ( $p=0,007$ ), IVS and HF ( $p=0,013$ ), and positive correlation between IVS and HOMA-IR ( $p=0,042$ ), and BP drop ( $p=0,010$ ). These suggest that IR may be involved in the severity of CAN and cardiac autonomic dysfunction in the pathophysiology of cardiovascular complications in these disease.

## **Ophthalmologic Findings in Congenital Generalized Lipodystrophy: A Possible Marker of Metabolic Disorders**

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**Background and aims:** Metabolic disorders can present ophthalmologic changes. Congenital Generalized Lipodystrophy (CGL) is characterized by severe metabolic manifestations such as insulin resistance, diabetes and hypertriglyceridemia, but there are few data published about ophthalmologic findings in this condition. This study aims to describe ocular abnormalities in patients with CGL.

**Materials and methods:** A cross sectional study with 15 patients with CGL of both sex, aged between 2 and 29 years old. We evaluated the symptoms of surface eye disease, visual acuity, the anterior segment of the eye, the break up time of the tear film with fluorescein, the corneal findings and the eye fundus.

**Results:** 15/15 (100%) subjects had hypertriglyceridemia; 15/15 (100%) low HDL-c; 4/15 (26,7%) high levels of LDL-c, 7/15 (46,7%) had diabetes. Symptoms of surface eye disease (blurred vision, pruritus, hyperemia or dry eye sensation) were presented in 9/15 (60%) patients and 8/15 (53%) had refractive errors: 5/8 (62,5%) astigmatism, 2/8 (25%) myopia and 1/8 (13%) myopia and astigmatism. In the slit lamp, 12/15 (80%) presented anterior blepharitis (seborrheic or meibomite), 13/15 (87%) decrease in the break up time of the tear (less than 8 seconds) and 5/15 (33,3%) keratitis. In the fundoscopy, 2/15 (13,3%) presented retinopathy (one with nonproliferative diabetic retinopathy and another presented proliferative diabetic retinopathy). Conclusion: CGL patients had high frequency of blepharitis and its complications, even in young subjects without diabetes. The presence of abnormalities in the anterior segment of the eye may be a marker of metabolic disorders as dyslipidemia and insulin resistance.

## Skeletal Muscle Dysfunction and Metabolic Abnormalities in Individuals with Familial Partial Lipodystrophy is Associated with Diminished Mitochondrial Fatty Acid Oxidation.

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### *Body:*

**Background:** Familial Partial Lipodystrophy, Dunnigan variety (FPLD) is characterized by post-natal loss of peripheral subcutaneous fat leading to severe insulin resistance and increased prevalence of diabetes. Affected individuals also display striking skeletal muscle hypertrophy, but there is limited information on muscle function and energy metabolism. We therefore systematically investigated muscle and mitochondrial function in 6 individuals with FPLD (2M, 4F with mean age  $43.2 \pm 17.9$  y) and 6 matched controls.

**Methods:** Body composition and intramyocellular lipid content (IMCL) were assessed by DEXA and magnetic resonance spectroscopy, respectively. Maximal voluntary strength and fatigue were assessed for both recumbent leg press and seated chest press. Vastus lateralis muscle biopsies were obtained prior to and following a high fat (40%) mixed-meal. Oxygen consumption in isolated mitochondria was measured using substrates supporting carbohydrate or lipid-based respiration. Insulin Sensitivity Index (SI) was calculated by minimal modelling.

**Results:** Individuals with FPLD had significantly lower SI, lower body fat content, and higher lean mass. Peak leg press and chest press force were not different, but FPLD individuals had earlier fatigue during chest press (number of repetitions:  $15 \pm 0.6$  vs  $20 \pm 0.3$ ,  $p = 0.01$ ). They also had a 50-60% decrease in state 3 respiration measured using substrates supporting lipid-based respiration ( $p = 0.04$ ). Further, mitochondrial oxidative capacity showed a strong correlation with muscle fatigue ( $r = 0.76$ ,  $p = 0.003$ ), and inversely correlated with fasting and post-prandial lipemia and measures of insulin resistance.

**Conclusion:** Individuals with FPLD have higher lean body mass and lower insulin sensitivity. Despite preserved peak muscle strength, they demonstrated earlier muscle fatigue. Decreased mitochondrial fatty acid oxidative capacity, likely related to elevated IMCL, may contribute to muscular and metabolic abnormalities.

## Evaluation of Hepatic Steatosis and Fibrosis Using Transient Elastography in Familial Partial Lipodystrophy

**Introduction:** Familial Partial lipodystrophy (FPL) is a rare disease associated with insulin resistance and metabolic dysfunctions, including non-alcoholic fat liver disease (NAFLD). Global estimated prevalence of NAFLD is 25% and remains unclear in FPL.

**Aims:** To evaluate the presence of hepatic steatosis and fibrosis in FPL using transient elastography (TE) in comparison to a control group.

**Materials and Methods:** Fifteen patients with FPL, including 8 with *LMNA* mutation, and 15 controls paired to BMI and age were included. Participants were 18 to 65 years-old and presented  $BMI \geq 25$  and  $\leq 35\text{kg}/\text{m}^2$ . Other causes of steatohepatitis were excluded. Anthropometric and metabolic parameters were evaluated. Liver Stiffness Measurement (LSM) and Controlled Attenuation Parameter (CAP) were analysed using TE(Fibroscan®) to estimate presence of hepatic steatosis/fibrosis. Student t-test was used for continuous variables.

**Results:** Mean age was 52.93 and 50.26 years-old in FPL and control groups, respectively. BMI was slightly higher in control group ( $30.13\text{kg}/\text{m}^2$  [ $SD \pm 2.85$ ] vs.  $27.43\text{kg}/\text{m}^2$  [ $SD \pm 5.30$ ]). FPL group had higher fasting plasma glucose ( $116.78\text{mg}/\text{dL}$  [ $SD \pm 39.54$ ] vs.  $89.58\text{mg}/\text{dL}$  [ $SD \pm 23.34$ ],  $p = 0.0476$ ). No differences in hepatic lesion biomarkers or lipid profile was noted, except for lower HDL-c in FPL group ( $40.64\text{mg}/\text{dL}$  [ $SD \pm 9.45$ ] vs.  $49.62\text{mg}/\text{dL}$  [ $SD \pm 12.67$ ],  $p = 0.0432$ ). CAP tended to be higher in FPL patients [ $301.82\text{dB}/\text{m}$  ( $SD \pm 54.88$ ) vs  $262.93\text{dB}/\text{m}$  ( $SD \pm 57.44$ );  $p = 0.0685$ ] and LSM was significantly higher ( $7.32\text{kPa}$  [ $SD \pm 3.71$ ] vs.  $4.94\text{kPa}$  [ $SD \pm 1.58$ ],  $p = 0.0260$ ).

**Conclusions:** Patients with FPL presented a trend for increased hepatic steatosis and significantly higher levels of liver fibrosis (LSM) in comparison to a control group. Further studies are necessary to evaluate NAFLD in FPL.

# DRAFT CONSENSUS DOCUMENTS

# PATHWAY TOWARDS GLOBAL COLLABORATION

## I. Working towards uniform data collection

- Reach a Consensus on Disease Classification.
- Establish working group (s) to review key distinctive features (presentation, morphomic characteristics and biomarkers) for each disease subtype
  - Decision on how to structure the working groups (by disease subtype or data subtype)
- Establish a working group for harmonization of existing databases in different centers
  - Decision on key data elements that are essential to collect longitudinally

## II. Early steps for global collaboration

- Create a website that will unite all centers studying lipodystrophy in a virtual network
- Build a data warehouse to link existing resources in research, advocacy and information
- Run quarterly case discussions or data clubs on the web
- Exchange visitor scholars across centers

## III. Improving understanding of natural history of diseases with lipodystrophy

- Ensure uniform method of presentation of patient level data on clinical studies
- Ensure clinical trials publish baseline state with complete data sets on patient characteristics, history, comorbidities, symptoms and signs.
- Build multi-system evaluations and PRO-tools into the trials.
- Working group to design prospective natural history studies

## IV. Evaluation of self-image, psychological well-being and physical functional state of patients

- Establish funding for a scholar position to research these elements of disease presentation who will undergo training and will be tasked to develop tools for further investigations.

## V. Creation of a clinical trial network to test novel therapeutics in a rapid manner with the best possible and efficient trial design

- Strategic inventory of strengths at each site
- Account of patients actively followed at each site
- Plan for keeping data current at each site

## **VI. Increasing awareness and advocacy:**

*Broad goals:*

- Recognition of Lipodystrophy Diseases as unique Rare diseases distinctive from common forms of metabolic disease
- Insurance coverage for specialty care, genetic testing and niche therapies

*Awareness Projects:*

- Art project: UM Art School and an Ann Arbor Artist will work with the patient community to create artwork on visual stories of lipodystrophy.
  - Unveiling of the art work in fall 2019,
- Engage a globally known brand to endorse awareness efforts
- Develop and transmit patient stories across global stages.
  - Patient stories will be recorded throughout the Symposium
    - Furthering collaborations with Global Genes and other advocacy platforms
  - Example patient story
    - <https://youtu.be/mjxvMlm9Y9M>

# CLASSIFICATION OF LIPODYSTROPHY DISEASES

## A. PRIMARILY METABOLIC DISEASES

### Generalized Lipodystrophy Syndromes

- **Congenital Generalized Lipodystrophy**
  - CGL1 (BSCL1/AGPAT2)
  - CGL2 (BSCL2/Seipin)
  - CGL3 (CAV1)
  - CGL4 (PTRF)
  - Other rare monogenic forms
  - Unknown
- **Generalized Progeroid Lipodystrophy with onset in childhood**
  - LMNA related
    - pT10I variant previously reported as idiopathic acquired generalized lipodystrophy in some cases
  - Others
- **Acquired Generalized Lipodystrophy**
  - Lipodystrophy syndromes with immune dysfunction
    - Associated with distinctive immunodeficiency
    - Other
  - Inflammatory lipodystrophy syndromes
    - Panniculitis-associated lipodystrophy

### Partial Lipodystrophy Syndromes

- **Polygenic Partial Lipodystrophy (Kobberling variety, or FPLD1)**
- **Familial Partial Lipodystrophy**
  - FPLD2 (LMNA)
  - FPLD3 (PPARG)
  - FPLD4 (PLIN1)
  - FPLD5 (CIDEc)
  - Other Extremely Rare forms
    - FPLD6: AKT2
    - FPLD7: PCYT1A
    - Other monogenic forms (ie ADR2A etc)
  - Unknown (FPLDX)

- **Familial Partial Lipodystrophy with lipomatosis**
  - **Symmetric Multiple Lipomatosis**
    - MFN2 related
      - With CMT Neuropathy
      - Without CMT Neuropathy
    - Others
  - **Asymmetric Lipomatosis**
    - LIPE related
    - Others
- **Acquired Partial Lipodystrophy**
  - Cephalocaudal (Barraquer-Simons syndrome)
  - Treatment- associated lipodystrophy
    - Corticosteroid-associated
    - HIV-antiretroviral-associated
    - Ethanol induced lipodystrophy with multiple symmetric lipomatosis
    - Total body irradiation-associated
    - Chemotherapy associated
    - Others
- **Unknown Partial Lipodystrophy**

## B. COMPLEX PHENOTYPE WITH ACCOMPANYING METABOLIC MANIFESTATIONS

### Monogenic Autoinflammatory Lipodystrophy Syndromes (can present with partial or generalized lipodystrophy)

- JMP syndrome: *PSMB8*
- CANDLE syndrome: *PSMB8*

### Progeroid Lipodystrophy Syndromes (can present with partial or generalized)

- Hutchinson-Gilford progeria
- Mandibulo-acral dysplasia
- Atypical LMNA-linked progeroid lipodystrophy syndromes
- MDP syndrome: *POLD1*
- Other monogenic progeroid lipodystrophy syndromes
  - *WRN, FBN1, BANF1, KCNJ6, SPRTN, CAV1*
- Unknown

### Other Syndromes Associated with Lipodystrophy

- SHORT syndrome: *PIK3R1*
- Complex mitochondrial diseases
- Others (e.g. congenital glycosylation defects)

# LOGISTICAL INFORMATION

# DIRECTIONS TO ROSEN CENTRE HOTEL

## Directions from the Airport to the Hotel

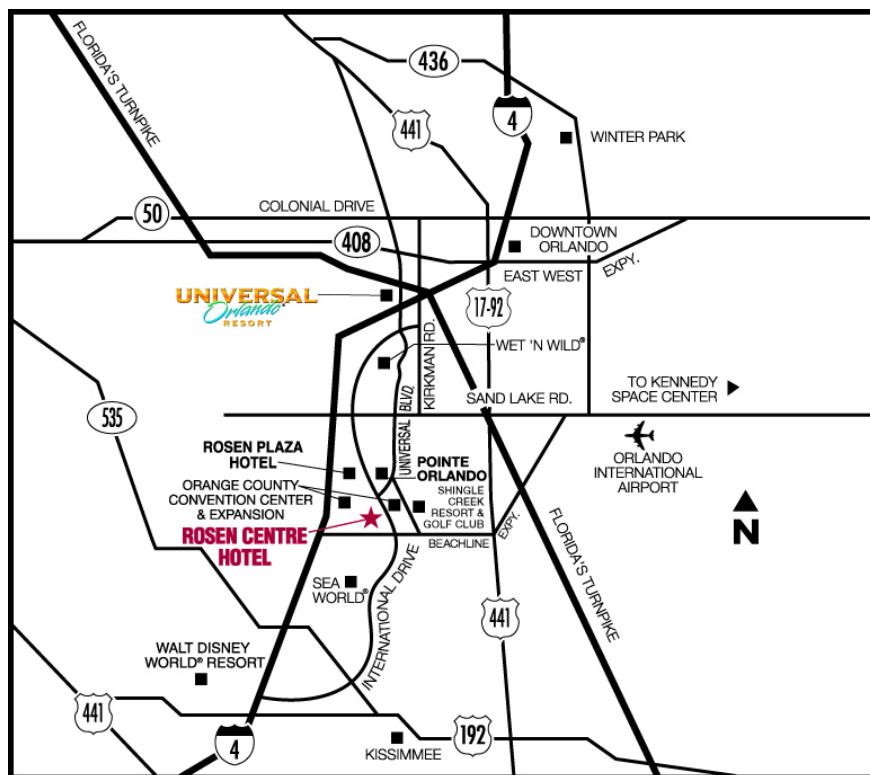
- Take the North exit from the airport
- Take SR 528 West (the Beeline Expressway)
- Take the International Dr./SeaWorld exit from the Beeline
- At the end of the exit ramp, bear right on International Dr.
- The Rosen Centre® Hotel is about a 1/4 mile on the left

## Directions coming from Tampa heading East on I-4

- Take I-4 East to Exit 72, (Beeline Expwy-SR 528) (also the International Airport Exit)
- Once on SR 528, take the first exit (International Dr. SeaWorld® Exit)
- Bear right on International Dr.
- The Rosen Centre® Hotel is about 1/4 mile on the left

## Directions coming from Daytona Beach or Orlando, Heading West on I-4

- Going West on I-4 take Exit 72 (Beeline Expwy-SR 528)
- Take the first exit (International Dr. and SeaWorld)
- At the end of the exit, turn right on International Dr.
- The Rosen Centre® Hotel is about 1/4 mile on the left, just before the Convention Center



Rosen Centre Hotel Address:  
9840 International Drive  
Orlando, FL 32819

Hotel Phone Number:  
(407) 996-9840

# SHUTTLE INFORMATION

Please refer to the following schedule for transport between

**Clarion Lake Buena Vista Hotel and Rosen Centre Hotel**

Date	Time	Departs From	Destination
Tuesday June 26 <sup>th</sup> , 2018	2:20 PM	Clarion Lake Buena Vista Hotel	Rosen Centre Hotel
	10:00 PM	Rosen Centre Hotel	Clarion Lake Buena Vista Hotel
Wednesday June 27 <sup>th</sup> , 2018	10:00 AM	Clarion Lake Buena Vista Hotel	Rosen Centre Hotel
	5:30 PM	Rosen Centre Hotel	Clarion Lake Buena Vista Hotel

# CONTACT INFORMATION

## The Rosen Hotel

9840 International Dr.  
Orlando, FL 32819  
(407) 996-9840

## The Clarion Buena Vista Hotel

8442 Palm Pkwy  
Lake Buena Vista, FL 32836  
(407) 996-7300

## Emergency Contacts

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# NOTES

# NOTES



# Lipodystrophy United

“I look through the texts and photos, thinking ‘that’s me’ It’s a really nice feeling to know I’m not alone...”

- Patient with FPL

## WHO WE ARE

Lipodystrophy United (LU) is an organization of committed individuals living strong with lipodystrophy. Our mission is to provide an interactive community, facilitating support and education for anyone affected by this rare disease. We serve as a resource and to increase awareness in the general population as well as the medical and insurance communities. We advocate and act as a catalyst for new patient diagnosis by assisting healthcare professionals in the understanding of lipodystrophy trends, physical attributes and clinical symptoms in order to aid in the advancement of knowledge, treatment and future research.

“When my child was 1, I was able to meet 4 patients with 2 different mutations of CGL. The feeling was overwhelming for a parent who knew nothing of the disease.”

-Parent of child with CGL

## WHAT WE DO

As a group of volunteers, LU is dedicated to meeting our communities' needs in the US and globally . We provide an informational website that includes education, patient stories and links to partners and research. We connect patients to each other and to physicians around the world. We provide subtype specific community advisors who assist patients with emotional support and guidance as they navigate difficult issues such as communicating with medical professionals not aware of lipodystrophy (LD) or problems with insurance. LU provides daily updates to the com-munity via social media including new research or community awareness activities. We answer all inquiries that come our way and if we don't have the answers, we will help you find them. In addition, we actively parti-ci-pate in advocacy training and partner with the greater rare disease com-munity.



[www.LipodystrophyUnited.org](http://www.LipodystrophyUnited.org)  
[www.RareConnect.org/Community/Lipodystrophy](http://www.RareConnect.org/Community/Lipodystrophy)

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