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LBN 01 - Interval of Enzymatic Activity of Phosphomannose Isomerase in a Sample of 32 Controls of 0.6-27 Years of Bogota-Colombia

Adis Ayala Fajardo¹, Jhoan Andres Samaca Martin¹, and Alfredo Uribe²

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The glycosylation defects type Ib (CDGIb) is an autosomal recessive inherited disease and are due to the deficiency of the cytoplasmic phosphomannose isomerase enzyme (PMI, EC 5.3.1.8), which catalyzes the interconversion between fructose-6-P and mannose-6P, controlling the endogenous production of this last molecule, indispensable in the mechanism of N-glycosylation of proteins. This disease is characterized by hepatic failure, hypoglycemia with hyperinsulinemia and coagulopathies with thrombosis, cerebrovascular accidents, hemorrhages, liver fibrosis, and enteropathy with protein loss.

The present work had the objective to determine values of reference of PMI-specific enzymatic activity. For that, a microspectrophotometric diagnostic method was standardized, starting from 32 samples with ages of 0.6 to 27 years, 14 of female gender and 18 the male gender, from which the leukocytes were extracted by the dextran-heparin method from whole blood. These were lysates by sonication, and the protein was quantified by the Folin-Lowry method, for which 2 assays were performed in a final volume of 300 μL using final concentrations of 0.6 and 1 U of the auxiliary enzymes PGI and G6PDH and tested 2 concentration of substrate 0.6 and 6 mM of M6P. The coenzymes and cofactors were maintained constant on the reaction mixture (0.6 mM NADP⁺, 10 mM MgCl₂ in buffer, and 100 mM HEPES pH 7.1), and the increased absorbance of the samples was read at 340 nm for 2 hours at 37°C in microplate reader VariosKan Flash. The best activity was obtained with 1 U of the auxiliary’s enzymes PGI and G6PDH and 6 mM of substrate Man 6 P. Our statistical analysis didn’t find a significant difference in enzyme activity by gender nor age, finding a P value of .3954 with a t value of .8623 and finding a P value of .6788 with an F value of .3926, respectively. The specific activity was higher with respect to other studies, 2416 nmol/h mg of protein. This study will allow initiating the diagnosis of patient’s deficiency of the phosphomannose isomerase at an early age and give an opportune diagnosis. Also, this disease offers an easy treatment and a low cost, which makes it a possible candidate enzyme for neonatal screening tests. In addition, the clinical diagnosis of this metabolic defect will benefit the patient and his family improving their quality of life, as well as the Colombian health system.

LBN 02 - Improvements in Cardiac Mass With Long-Term Migalastat Treatment in Patients With Fabry Disease: Results From Phase 3 Trials

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Cardiac complications (eg, heart failure, myocardial infarction) are the main cause of death in patients with Fabry disease, a rare X-linked disorder of lysosomal a-galactosidase A deficiency that causes lysosomal deposition of globotriaosylceramide. A progressive increase in left ventricular mass index...
(LVMi) is generally observed across disease phenotypes, and the effect of enzyme replacement therapy (ERT) on LVMi in patients with Fabry disease has been variable. Changes in cardiac parameters with long-term migalastat treatment were assessed in patients with Fabry disease treated in phase 3 clinical trials. In FACETS (NCT00925301), 67 ERT-naive patients were randomized to 6 months of migalastat 150 mg once daily or placebo, followed by 18 months of migalastat; 54 patients continued migalastat in a separate open-label extension (OLE; NCT01458119). In ATTRACT (NCT01218659), 60 ERT-experienced patients were randomized to 18 months of migalastat or ERT, followed by 12 months of migalastat. The effect of migalastat on cardiac mass was assessed by echocardiogram (blinded, central review) and is reported for patients in the intention-to-treat population who had amenable mutations. After 18 or 24 months of migalastat treatment in FACETS (18 months for patients initially randomized to placebo, 24 months for patients randomized to migalastat), there was a statistically significant mean change from baseline in LVMi (−7.7 g/m²; 95% confidence interval [CI]: −15.4 to −0.01; n = 27). Among patients who entered the OLE, further reductions were seen (month 30/36: −17.0 g/m²; 95% CI: −26.2 to −7.9; n = 15), including statistically significant changes in patients with left ventricular hypertrophy (LVH) at baseline (−20.8 g/m²; 95% CI: −37.4 to −4.1; n = 11); 82% (9/11) had reductions and 45% (5/11) had normalizations of LVMi. Similarly, LVMi was reduced in patients treated with migalastat in the ATTRACT trial. At month 18, mean changes from baseline were −6.6 g/m² (95% CI: −11.0 to −2.1; n = 31) with migalastat and −2.0 g/m² (95% CI: −11.0 to 7.0; n = 13) with ERT. Patients treated with migalastat continued to show reductions in LVMi at month 30 (−3.8 g/m²; 95% CI: −8.9 to 1.3; n = 30). Among those with baseline LVH (n = 13), LVMi was reduced by −9.0 g/m²; 85% (11/13) had reductions and 31% (4/13) had normalizations of LVMi. In patients with Fabry disease and amenable mutations, long-term migalastat treatment was associated with sustained reductions in LVMi and regression of LVH.

These infants are hypothesized to have a normal physical examination and structurally normal brain imaging, and we characterize this as a non-Mendelian, nondysmorphic (NoMeND) form of autism. These infants are hypothesized to develop deficiency of carnitine and perhaps other nutrients in the brain causing autism that may be amenable to early reversal and prevention through dietary supplementation with carnitine. A mixed, common gene variant-environment hypothesis is proposed with diet, minor illnesses, microbiome, and drugs as possible risk modifiers. We searched for a carnitine-related explanation for the high male/female ratio and found that a gene on the X chromosome in humans and mice (SLC6A14/Slc6a14) is likely escapes random X-inactivation based on the absence of differential methylation on the inactive X chromosome in both species. The SLC6A14 protein is an amino acid and carnitine transporter that functions at the blood–brain barrier (BBB). The lack of X-inactivation could lead to greater expression in females than males at the BBB and could limit transport of carnitine across the blood–brain barrier in boys compared to girls. We assessed transport across the BBB in mice by tail vein injection of [14C]-carnitine. At 4 hours, transport to the brain was greater in wild-type female mice compared to male mice, likely due to lack of X-inactivation of Slc6a14. Transport of [14C]-carnitine across the BBB is reduced in female and male Slc6a14 null mutants compared to wild-type mice. These data suggest that Slc6a14-mediated transport across the BBB is greater in female compared to male mice. We propose that differences in carnitine transport across the BBB may contribute to metabolic sexual dimorphism of the brain in mammals, possibly explaining the extremely high male/female ratio in nonsyndromic autism via susceptibility to brain carnitine deficiency. Perhaps the lack of any Recommended Dietary Allowance for carnitine in infants should be reviewed.

LBN 04 - Mucopolysaccharidosis: A Look at Prevalence in Pernambuco State

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Rare diseases still represent a challenge for Brazilian public health system. Around 95% of the affected ones don’t have access to specific treatment and depend on a well-structured palliative medical care network (Brazil, 2015). Knowing this, this study aims to describe and analyze the expected number of mucopolysaccharidosis patients (MPS), a rare disease, subtypes I, II, IV and VI, with the number of patients already diagnosed, in Pernambuco state, northeast of Brazil. Intending a better universality and integrality, for these patients, of SUS (Sistema Único de Saúde), “HealthUP”, an iOS and Android App was used as the data collection instrument to the diagnosed

LBN 03 - SLC6A14-Mediated Higher Blood–Brain Barrier Transport of Carnitine in Females: Relevance to the Metabolic Sexual Dimorphism of Brain and the Extreme Male/ Female Ratio and in Milder Autism

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The purpose of this study was to partially test the hypothesis that brain carnitine deficiency may cause 10% to 20% of all autism as recently proposed (PMID 28703319). This hypothesis involves nonsyndromic or “essential” autism with an extremely high male/female ratio in infants who are genetically normal except for common or low penetrance genetic variants.

Beregaming differs in terms of gender and neurological conditions. The climbing rate of obesity and undernutrition in Brazil is also contributing to the growth of the disease burden in this population. Therefore, the purpose of this study is to provide a better understanding of the prevalence of rare diseases.
patients. The data, obtained from the NGO Breno Bloise Institute, were 2 patients with MPS type I, 12 patients with MPS type II, 14 patients with MPS IV, and 32 patients with MPS type VI. The total number of 60 patients were diagnosed in Pernambuco, for the 4 MPS subtypes analyzed. Checking the most recent data of Rede MPS Brazil, it is estimated approximately 1 out of 100 000 newborn MPS I and II, 1 out of 25 000 newborn, and about 1 out of 200 000 newborn have MPS VI. Finally, according to IBGE 2014 data, there are 9 278 000 inhabitants in Pernambuco. Analyzing the data between the diagnosed patients and the possible patients in Pernambuco, one can detect that the number of possible patients to MPS I and II is 186, but only 14 were diagnosed until now. To MPS IV, there are 371 possible patients, but only 14 were diagnosed. At last, to MPS VI, there are 46 possible patients, and only 32 were diagnosed. In summary, it was possible to describe and analyze the number of possible patients with the diagnosed ones in Pernambuco. Moreover, it was possible to realize that to the MPS types I, II, and IV, the number of diagnosed patients doesn’t correspond to the expected number. However, to MPS VI, the rarest subtype, the numbers are closer, there are 46 possible patients and 32 diagnosed ones. Therefore, to a better universality and integrality of SUS, there is a need of future searching for identification, diagnose and medical care to the MPS types I, II and IV. In the next stage of the study, analyses of the distribution of patients in stratified regions of the state of Pernambuco will be carried out, allowing the crossing with data from other databases, as well as allowing for planning other intervention actions. The analyses, always supported by App HealthUP, can also be extended to other states.

LBN 05 - Geographic Information of MPS Patients

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The decision-taking has complex political, technic, and administrative determination. Information can contribute to help political decision to be closer to the real population needs and according to the principles and guidelines of SUS (Sistema Único de Saúde; Junior 2013). Soon, this research has the purpose of analyzing the patients geographic position of the rare disease: mucopolysaccharidosis (MPS) type I, II, IV, and IV in Pernambuco. Providing the identification of priority places to “screening” population, political decision and local planning to implementation of infusion centers. HealthUP was used to collect the patients geographic information, built by public health, computer, and medical scientists. Moreover, the geographic position, the data collection instrument has helped in order to achieve other 25 information field, including images. The data collection was released through the help of NGO called Breno Bloise Institute whose mission is to promote integral assistance to people with rare diseases. The data collected by the Breno Bloise Institute was: 2 patients with MPS type I, 12 patients with MPS II, 14 patients with MPS IV, and 32 patients with MPS type VI. These patients are divided into 5 Pernambuco mesoregions, which are São Francisco, Sertão, Agreste, Zona da Mata, and Recife mesoregion. The same way, the collection instrument is still able to make filtration and patients observation with specific pathology, in a specific region, no matter if it is in a county, mesoregion, and state. It is still possible to analyze the data in file type .xls. To sum up, in the research, it is possible to analyze information about patients with the rare disease MPS, starting from a data collection instrument that helped to visualize and analyze the patients’ geographic position in the Brazilian map. Soon, starting from this georeferencing, new analysis can be done in order to increase Pernambuco’s political decision power about SUS. Moreover, other researches can be made in order to identify priority places to populational screening as places to have the infusion centers installation.

LBN 06 - Quantitative Analysis for Newborn Diagnosis in Plasma of Aminoacidopathies Using LC-MS/MS

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The quantitation of amino acids from biologic samples has become an essential method for monitoring and diagnosing patients with inherited metabolic disorders. The study’s objective was the development of a new nonderivatized method, rapid and sensitive, for quantification of 11 amino acids in plasma by exploring a high-resolution liquid chromatographic separation with electrospray ionization (ESI) mass spectrometry detection. Only 20 µL of plasma was used in an extraction with a mixture of methanol and 0.1% formic acid containing stable isotopically labeled internal standards and analyzed by an HPLC system using an HILIC amide, 4.6 mm × 100 mm, 3.5 µm column. The Waters TQ Detector mass spectrometer was employed for detection of amino acids using multiple reaction monitoring (MRM) optimized. A phase gradient was used applying 0.1% formic acid in water for mobile phase A and 10 mM ammonium acetate in 90:10 acetonitrile/water for mobile phase B. The total run time was 30 minutes per sample considering also re-equilibration. The correlation coefficients were greater than 0.995 for all amino acids. This method could be used as a gold standard test for newborn screening of specific disorders associated with high levels of amino acids, monitoring, shortening the time to diagnosis, and significant reduction in false-positive cases. In addition, the chromatographic separation enables for assessment of MSUD by separating leucine and isoleucine.
LBN 07 - Lipidomics as a New Tool to Identify Unrecognized Defects in Fatty Acid Homeostasis

Benoit Colsch
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Essential to the integrity of cell membranes, lipids also have many biological functions linked to energy storage and cell signaling and are involved in a large number of heterogeneous diseases such as cancer, diabetes, neurological disorders, and inherited metabolic diseases. Due to the high structural diversity of the lipidome, the simultaneous detection of minor and major lipid species using mass spectrometry remains a challenge. The presence of multiple isobaric and isomeric lipid species in addition to the presence of numerous distinct lipid classes increases the complexity to characterize the lipidome in complex biological matrices. The development of methods based on mass spectrometry (MS) has rapidly expanded over the last 2 decades with direct introduction methods named “shotgun lipidomics” or hyphenated methods such as liquid chromatography (LC-MS) or supercritical fluid chromatography (SFC-MS). Along with the evolution of mass spectrometry instrumentation, bioinformatic tools have been developed in the fields of lipidomics to handle process and interpret large amounts of data. With the emergence of high-resolution MS and the instrumentation capability to perform simultaneous analyses (MS and MS/MS experiments), the major challenge now using untargeted lipidomic approaches is to deal with the vast amount of information generated by the data acquisitions and the available databases for lipid annotations in order to better understand lipid pathways impacted in various studied diseases.

LBN 08 - PSAP Gene Analysis: A Possible Alternative Pathway for Gaucher Disease

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Gaucher disease is a rare autosomal recessive disorder caused by the deficiency of the lysosomal enzyme β-glucocerebrosidase (GBA), which metabolizes the glycolipid glucosylceramide (GlcCer) to ceramide and glucose. Gaucher disease is presented in 4 types (I, II, III, and perinatal lethal form), with signs and symptoms that may vary widely among affected individuals. The observed phenotypic variability in this disease has led to a search for alterations in genes that could function as Gaucher modifiers. According to the literature, the deficiency in saposin C, an essential activator for GBA, due to mutations in PSAP, results in a Gaucher-like phenotype, but this form of the disease is very uncommon with few cases described. Our objective is to evaluate the GBA and PSAP genes variants, correlating the results with phenotype. In this work, we analyzed 23 individuals with Gaucher symptoms without mutations in GBA gene that could explain the symptoms. The sequencing analysis of GBA and PSAP (RefSeqs NG_009783, NG_009301) showed 3 patients with the variant p.N409S (c.1226A>G) heterozygous in GBA gene in addition to the variant 5′ UTR c.-4C>T in PSAP gene, 2 in heterozygosis and 1 in homozygosis. These results show that Gaucher can be a nonmonogenic disease and create a possible differential diagnosis. Financial support: CNPq and FAPESP (Process 2014/27198-8).

LBN 09 - Hematopoietic Stem Cell Transplantation for MPS I: Experience of 3 Brazilian Centers

Carolina Fischinger Moura de Souza, Roberto Giugliani, and Filippo Vairo
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Hematopoietic stem cell transplantation (HSCT) has been a successful strategy for the treatment of Hurler syndrome (MPS I severe form, or MPS-IH). HSCT corrects the enzyme defect in white blood cells of patients with MPS-IH, although it does not provide complete clinical recovery. The fatal complications may be prevented, and MPS-IH children treated with HSCT generally have an increased lifespan compared to untreated children. Report of the experience of 3 Brazilian centers with HSCT for MPS-IH. HSCT was performed in 8 MPS-IH patients over a period of 6 years (2010-2016): 4 males and 4 females were transplanted in 2 different centers in Southern Brazil (Curitiba and Porto Alegre); all patients were homozygous for p.W402X mutation; age at diagnosis ranged from 1 to 22 months of life; age of HSCT ranged from 8 to 28 months of age; 7 of 8 patients received ERT with laronidase from 10 to 24 months before the HSCT; in 5 of 7 cases, the donor was an HLA-matched unrelated volunteer. The conditioning regimen consisted in the association of busulfan and cyclophosphamide with mesna. Rabbit -derived antithymocyte globulin to prevent graft rejection was used in combination with the conditioning regimen only in HSCT from unrelated donors. Primary graft failure was observed in 6 of 8 patients. Three patients have died, 1 received a second transplant. The primary cause of death was infection in 2 cases and disease progression in the other patient, after primary graft failure. Regarding the 3 living patients, 1 received 3 transplants and had severe disease progression after graft failure and the other has functional grafts with a favorable long-term outcome after a median follow-up of 5 years, presenting mixed chimerism (30%). Despite the low chimerism, the patients have had improvements in motor skills, language, and brain lesions. Dysostosis multiplex has progressed. The outcome of HSCT for MPS-IH has not been favorable in the experience of these 3 Brazilian centers. The reasons for this probably are: the diagnosis of MPS has been performed late, the waiting time for HSCT has been long, lack of an unified protocol with the indications of the procedure, and how to follow up MPS patients. But patients with favorable outcome have noticed the stabilization of the disease progression, normalized
biochemical parameters, and have had a better neurological development, although the bone dysplasia progressed.

LBN 10 - Lethal Acute Rhabdomyolysis as a Presenting Symptom of X-linked Adrenoleukodystrophy

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Genetic disorders that result in death pose a difficult challenge, as the cause of death often remains unknown. The family is left with unanswered questions and other affected children or family members may be at risk. Here we present an 8-year-old male whom experienced a series of unexplained illnesses over a 2-year period prior to his death. During this time, he had 6 episodes of acute illness requiring hospital care, each characterized by severe headache, emesis, dehydration, and severe rhabdomyolysis. During his last episode, rapid deterioration in his condition prompted transfer to the ICU. A head CT showed bilateral cerebral edema with herniation. His neurologic exam met established criteria for brain death, and after consultation with the family, artificial life support was discontinued and the child died. The parents consented to an autopsy. Generalized hyperpigmentation was noted at autopsy. Gross and anatomic examination of the autopsy specimens showed bilateral abnormalities of the adrenal glands, suggestive of adrenoleukodystrophy (ALD). Due to rapid deterioration and imminent death, a whole exome sequencing was obtained along with routine biochemical studies. Whole exome sequencing identified an ABCD1 pathogenic variant previously reported in X-Linked adrenoleukodystrophy (ALD). ALD, a rare, X-linked disorder, is characterized by elevated levels of very long chain fatty acids (VLCFA) in the brain and adrenal cortex. Males are more often and more severely affected than females. Accumulation of VLCFA results in loss of myelin and progressive dysfunction of the adrenal gland. Primary adrenal insufficiency (AI) may manifest as nausea, vomiting, hyperkalemia, hyponatremia, and episodes of dehydration. ALD is typically debilitating or fatal within 2 to 5 years of onset. Other symptoms of ALD include deafness, blindness, muscle wasting, and dementia. Rhabdomyolysis is not a common presentation of ALD and therefore often an unrecognized symptom. Genetic testing avoids further misdiagnosis and allows discussions of treatment options of affected family members. In this case, the autopsy allowed family members to receive genetic counseling. This case illustrates the important role of whole exome sequencing and postmortem testing to confirm the cause of death.

LBN 11 - Glycogen Storage Diseases: The Latin American Landscape

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Glycogen storage diseases (GSD) are a group of classic inborn errors of metabolism that result from a deficiency in any one of several enzymes required for either glycogen synthesis or glycogen degradation. Classically, the GSD can be divided into those with hepatic involvement, which present as hypoglycemia, and those which are associated with neuromuscular disease and weakness. The severity of GSD has a broad spectrum, ranging from those that are fatal in infancy if untreated to mild disorders with a normal lifespan. A founder effect has been well described in individuals with glycogen storage disease Ia (GSD-Ia) of Japanese descent (c.648G>T, 85-88%), Ashkenazi Jewish descent (c.247C>T, 96%), and Hispanic descent (c.378_379dupTA, 50%). Further delineation of the Latin American landscape has not been described in detail. Emerging phenotypes and availability of next-generation sequencing panels indicate GSD may be more common than anticipated. The Latin America GSD profile will be discussed, as well as new avenues to continue to delineate the GSD Latin American landscape.

LBN 12 - Novel Insights Into the Transcytosis of Protein-Based Nanoparticles: A Possible Strategy for Brain Penetrant ERT

David Begley, Svetlana Drndarski, and Anne Iltsche
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Human serum albumin (HSA) nanoparticles, modified with apolipoprotein E (ApoE) or a polysorbate-80 coating, cross the blood–brain barrier (BBB) in vivo and are widely distributed in the brain after an intravenous injection. These nanoparticles are biodegradable and nonantigenic. Electron microscopy showed the brain intracellular localization of the surface-modified nanoparticles 15 minutes after intrajugular injection. Whereas unmodified HSA nanoparticles were not seen within the brain tissue. The BBB crossing ability of the modified nanoparticles is mediated by receptor-mediated endocytosis followed by transcytosis (RMT) involving the LRP1 receptor as has been demonstrated in vitro. However, the rapid rate of nanoparticle movement within the brain tissue remains surprising. Confocal microscopy confirmed electron microscopic findings, underlining the rapid movement of the modified HSA nanoparticles through the brain tissue following brain BBB endothelial cell internalization. Although only 0.05% of the injected dose of nanoparticles are present in the brain, this represents 239.8 million nanoparticles in the entire mouse brain at a rate of 2.2 particles per cell. This also represents a considerable quantity of protein. The aim of brain penetrant recombinant ERT is to include the CNS in the therapy. The fact that particles are distributed to the liver and spleen in addition to the brain is encouraging. With an average diameter of 200 nm, the nanoparticles are far too big to travel freely through the highly tortuous extracellular space of the brain. Furthermore, the modified nanoparticles were never observed extracellularly within the brain, except for the basal lamina. Astrocytic end-feet...
covering the brain endothelial cells are well positioned to internalize the nanoparticles and mediate further transport through the brain tissue. Known cytoplasmic flow rates of 2 to 16 mm/h could explain the rapid rate of intracellular movement observed. Furthermore, the modified HSA nanoparticles were highly concentrated in the astrocytic end-feet 5 minutes after injection, as shown by confocal microscopy, and localized in the distal astrocytic processes 15 minutes after injection, as shown by 3-D reconstruction. Within 30 minutes, the HSA nanoparticles are distributed within the cytoplasm of neurons. These observations lead to a reevaluation of the role of astrocytes in the rapid movement of large structures and molecules within the brain.

LBN 13 - POFUT1 Deficiency: A Candidate Syndrome Affecting Protein O-Fucosylation

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We report a patient with a potential novel syndrome with homozygous mutations in POFUT1 and functional studies showing a defect in protein O-fucosylation. The patient was the product of a consanguineous marriage who was seen at 4 years of age with a history of global developmental delay, failure to thrive with microcephaly, and congenital heart disease including severe coarctation of the aorta and ventricular septal defect. An MRI showed portal vein agenesis. Physical examination showed microcephaly, reduced fat pads, low set posteriorly rotated ears, wide-spaced nipples, and mild hypotonia. The patient had an elevated PT of 19.8 with low Factor II, VI, VII, IX, protein C, antithrombin III, and fibrinogen. Serum transferrin by isoelectric focusing was normal. CDG O-glycosylation showed elevated T-antigen 2.1 μmol/L (normal 0.22-1.14) and T-antigen/Sialyl T-antigen ratio 0.08 (normal 0.00-0.06). Chromosomal microarray was normal except for 103 Mb regions of homozygosity. Exome sequencing showed homozygous p.Ser162Leu mutations in POFUT1. The mutation alters one of 2 predicted N-glycosylation sequences in POFUT1. Fibroblasts from the affected patient had similar levels of POFUT1 mRNA and protein compared to controls. However, enzymatic activity of POFUT1 using a factor IX (FA9) EGF repeat with an O-fucosylation site was significantly lower in patient cells than in controls. Biochemical studies showed that the p.Ser162Leu mutant had a lower Vmax compared to wild type (1.43 nmol/min/mg vs 28.6 nmol/min/mg). The mutant enzyme had a higher Km for FA9 EGF (11.98 μmol/L versus 1.50 μmol/L), indicating the mutant enzyme has a lower affinity for the acceptor substrate. POFUT1 regulates Notch activity, and using cell-based Notch1 signaling assays in POFUT1-null U2OS cells, we demonstrated that the mutant POFUT1 rescued Notch activity to a much lower extent than control cells. In conclusion, our patient has a phenotype with some similarities to those seen in Notch defects, including congenital heart disease and vascular defects and neurogenesis. Some features such as absent fat pads and abnormal factor activity are reminiscent of other congenital disorders of glycosylation. This patient’s presentation and the functional studies of POFUT1 and Notch activity make a strong case that this is a new autosomal recessive congenital disorder of glycosylation. Supported by NIH GM061126 to RSH.

LBN 14 - Eryminase, Arginine Deiminase-Encapsulated Red Blood Cells Effectively Lower Blood Arginine Levels in a Mouse Model of Inducible Hyperargininemia

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Arginase deficiency is a rare genetic disorder affecting the final step of the urea cycle in liver that converts waste nitrogen in the form of ammonia into urea for excretion in the urine. This devastating disorder leads to profound neurological problems (spasticity of limbs, mental impairment, and brain atrophy). There are currently no cures, and treatment outcomes are usually poor with a low-protein diet and/or nitrogen scavenger drugs. The main biochemical feature is accumulation of arginine leading to toxic levels of guanidino compounds and nitric oxide. As an alternative treatment approach to reduce the toxic accumulation of arginine and its metabolic side products, we envisioned an innovative enzyme therapy. Eryminase is an arginine deiminase (ADI, bacterial protein from Mycoplasma arginini) entrapped in red blood cells using ERYTECH’s proprietary ERYCAPS technology platform to provide effective, long-acting therapeutic activity with reduced toxicity. ADI metabolizes arginine into citrulline, a nontoxic product, part of the urea cycle. PK and PD parameters of eryminase (encapsulated ADI in red blood cells) were first evaluated in healthy mice. Once entrapped into erythrocytes, one single injection of ADI triggers a complete plasma arginine depletion for 16 days. We are currently conducting experiments to demonstrate the potential of eryminase to lower blood arginine in a mouse model of tamoxifen-inducible arginase deficiency that shows the cardinal sign of hyperargininemia, as in humans (Sin et al. PLoS One. 8(11)). Eight days after tamoxifen injection, which effectively deletes exons 7 and 8 of the mouse Arg1 gene, blood levels of arginine were approximately 4 times greater (400 μM) than at baseline in all 4 groups of the study.
Abstracts

Preliminary results show that eryminase injected at 2 doses (4 and 8 mL/kg; groups 1 and 2; n = 5 each) reduced blood arginine levels, 24 hours after administration, by 52% and 92%, respectively, while mice injected with unloaded RBCs (group 3; n = 5) and non-RBC injected control (group 4; n = 6) showed unchanged or slightly elevated levels. Seventy-two hours later, blood arginine levels remained suppressed in mice of groups 1 and 2 by 19% and 74%, respectively. The data suggest that arginine deiminase loaded within erythrocytes may be an effective strategy to counteract the main biochemical defect of the rare genetic disorder of arginase deficiency.

LBN 15 - HMG CoA Synthase: A case and Unique Biochemical Markers

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We report an 8-month-old patient with decreased consciousness after a febrile episode and reduced oral intake. He was profoundly acidic, but his lactate was normal. Serum triglycerides were markedly elevated and HDL cholesterol was very low. The urine organic acid analysis during the acute episode revealed a complex pattern of fatty acid oxidation disorder, but plasma amino acids and acylcarnitine species were undiagnostic. An MRI showed extensive brain abnormalities concerning for a primary energy deficiency. Whole exome sequencing revealed heterozygotic HMGCS2 variants, a gene encoding for mitochondrial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase-2 deficiency 3-hydroxy-3-methylglutaryl-CoA synthase-2 deficiency 3-hydroxy-3-methylglutaryl-CoA 3-hydroxy-3-methylglutaryl-CoA 3-hydroxy-3-methylglutaryl-CoA 3-hydroxy-3-methylglutaryl-CoA 3-hydroxy-3-methylglutaryl-CoA HMG-CoA synthase-2 (HMGCS2), which catalyzes the irreversible and rate-limiting reaction of ketogenesis in the mitochondrial matrix. Autosomal recessive HMGCS2 deficiency is characterized by hypoketotic hypoglycemia, vomiting, lethargy, and hypomegaly after periods of prolonged fasting or illness. HMGCS2 synthesizes HMG-CoA, a precursor to ketone bodies, as well as mevalonate and cholesterol. The biochemical and molecular findings were unexpected as 3-hydroxybutyrate and acetoacetate were present in urine during crisis. A retrospective analysis of the urine organic acid analysis identified putative 4-hydroxy-6-methyl-2-pyrones, a recently reported biomarker of HMGCS2 deficiency. There was also a relative elevation of plasma acetylcarnitine as previously reported in one case. Our patient highlights a unique presentation of HMGCS2 deficiency caused by novel variants in HMGCS2. This is the first report of HMGCS2 deficiency with a significantly elevated triglyceride level and decreased HDL cholesterol level at presentation. Hence, HMGCS2 deficiency should be included in the differential diagnosis of individuals with coma induced by fasting or illness, and who present with hypertriglyceridemia, or low HDL cholesterol levels in childhood. Although HMGC2 deficiency is a rare disorder with unspecific symptoms, with the advent of next-generation sequencing, and the recognition of novel biochemical biomarkers, the incidence of this condition may become better understood.

LBN 16 - Ingestion of Triheptanoin-Containing Chow Improves Exercise-Associated Cardiac Muscle Anaplerosis in Murine VLCAD Deficiency

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Dietary odd-chain fatty acid supplementation has been suggested as a method to increase citric acid cycle intermediates CACi pools and energy metabolism in subjects with long-chain FAO disorders such as VLCAD deficiency. We investigated CACi depletion after exhaustive exercise and the ability of triheptanoin (C7) to increase CACi in murine VLCAD−/−. Wild-type (WT) or VLCAD knockout (VLCAD−/−) mice fed normal chow were monitored by indirect calorimetry (IC) at rest and during exercise. VLCAD−/− mice were exercised at 60% VO2 max to exhaustion or up to 60 minutes on a treadmill. WT animals were similarly exercised, and CACi was measured in cardiac tissue by stable isotope dilution targeted metabolomics (AB Sciex API 4000 tandem mass spectrometer). To investigate the effects of odd-chain supplementation at rest and during exercise stress, WT or VLCAD−/− mice were fed chow supplemented with triheptanoin (C7) or medium-chain triglycerides (MCT) at 30% of energy for 4 weeks; IC and cardiac CACi were measured as above. Resting VLCAD−/− mice fed normal chow have a similar respiratory exchange ratio (RER) but lower VO2, suggesting a similar substrate utilization but lower energy expenditure compared to WT mice. VLCAD−/− mice fed C7 or MCT had lower RER (increased fat oxidation) compared to normal chow counterparts and higher VO2, suggesting that both oils are oxidized and increase energy expenditure. Exercised VLCAD−/− mice fed normal chow exhaust far sooner than WT mice, but VLCAD−/− mice fed C7 or MCT exhaust at a similar rate to WT. VLCAD−/− mice exhibited lower succinate concentration in cardiac muscle at exhaustion than exercised WT and rested VLCAD−/−, suggesting decreased anaplerosis with prolonged exercise. However, exercised VLCAD−/− fed C7 exhibited higher cardiac malate and succinate than exercised VLCAD−/− fed MCT, suggesting that anaplerosis had been partially restored in C7-supplemented animals. Interestingly, metabolomics studies demonstrated accumulation of long odd-chain fats in C7 fed animals, suggesting that at least a portion of ingested C7 had been elongated to longer chain fatty...
acids rather than being exclusively oxidized. VLCAD−/− mice exhibited decreased cardiac succinate following exhaustive exercise. C7 supplementation led to increased cardiac malate and succinate suggesting a role for the administration of anaplerotic substrates in murine FAO disorder models. Funded by Ultragenyx Inc.

LBN 17 - Four Novel Mutations in the α-Galactosidase A Gene in Peruvian Families With Fabry Disease

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Introduction: Mutations in the α-galactosidase A gene (GLA) lead to Fabry disease (MIM 301500), an X-chromosomal inherited lysosomal storage disorder of the glycosphingolipids produced by deficit of lysosomal enzyme α-galactosidase A (α-GAL A). The Human Gene Mutation Database, Fabry mutation database, and Clin Var database have hundreds of mutations of GLA gene-encoding α-GAL A registered. The estimated incidence of Fabry disease is ~1 in 50 000 males in the world. Incidence in Peru has not been established.

Objective: To report 4 novel mutations in the GLA gene and the molecular characterization of 14 Peruvian families with Fabry disease. Methods: A screening program using α-GAL A activity in blood spot was performed in patients undergoing hemodialysis at the largest hospitals in Peru. In those people who had reduced enzymatic activity confirmed in leukocytes, complete sequencing of the GLA gene was performed. A family tree was built for each proband including all members of at least 4 generations. Enzymatic and molecular familial mutation targeted testing were performed in all available at-risk family members. Results: After screening, 16 patients presented reduced enzyme activity confirmed in leukocytes. Thirteen different mutant alleles were identified in these families; 3 mutations (p.D109G, p.K130T and p.R363H) are shared by 2 families. Four novel missense mutations were detected (p.G35A, p.I64F, p.K130T and p.G171S); one of these mutations is shared by 2 families. Family trees were built for 14 families with 1674 members; of which 446 members identified as subjects at risk of carrying a mutation were studied looking for their carrier familial mutation. One-third (n = 147) of them were carriers of their specific familial mutation. We found 52 (34%) heterozygous males and 95 (66%) hemizygous females. Twenty-two male patients and 1 symptomatic woman are actually undergoing enzyme replacement therapy (ERT). Conclusions: The complete molecular analysis of the GLA gene performed in 16 Peruvian families showed 13 different genotypes; 4 novel missense mutations were found. The identification of the familial mutation enables targeted investigation in all at-risk family members in order to identify symptomatic patients and recommend early enzymatic replacement treatment. Disclosure: Study sponsored by Sanofi-Genzyme.

LBN 18 - A Collaborative System to Support Communication Between Users Involved With Mucopolysaccharidosis VI

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The Internet, as we know, is a platform of great access, which nowadays millions of individuals connect to daily, everywhere on earth (Tapscott & Williams, 2007). People and some institutions take advantage of virtual systems to publicize and share online activities (Evans, 2009). These systems offer greater communication between people, strengthen social bonds, and create mutual aid systems or groups (Frey, 2000; Shirky, 2010). Health data, generated by a patient, are important and relevant to the definitions of health care. These data have the potential of impacting the patient–clinical relationship (Woods, 2016; Bradway, 2016; Katz, 2002; Petersen, 2016). The MPS VI has dysmorphic signs in the body due to the lack or deficiency of a certain enzyme in its lysosomes (Cardoso-Santos et al, 2008; Borges et al, 2003). The purpose of this work is, through a Technological Collaborative System, to be able to offer a communication channel to support the interaction between processes and users related to a screening and diagnosis of the MPS VI, generating comprehension about the disease from the distribution and propagation of information from the related area, understanding of therapeutic processes, understanding the impact of these processes on the quality of life of patients with MPS VI, and understanding the biological and treatment processes. For the development of this system, it was used, in all design thinking processes, the PDCA Cycle (Campos, 1992), offering a better quality of development in all stages of the project. Thus, it was possible to develop a collaborative system that supported the interested community, with the possibility of creating different types of information access groups, such as a group model, where users have access with a certain degree of control. At this level, only invited users will be able to join the group and their intention is to promote a solid relationship among the users, of which they are part. Another group model has completely restricted access. This access is only allowed for specific and determined guests. Where doctors could discuss, for example, subjects of more technical interest and patient data are confidential and protected. The collaborative system ultimately provides free access to other users, accessing content such as videos, useful websites, images, and so on, on basic information related to the topic, such as MPS VI.
LBN 19 - Founder Mutation and New Diagnosis Biomarker in a Large North African Cohort With PLA2G6-Associated Neurodegeneration (PLAN)

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Mutations in the PLA2G6 gene are causative of PLA2G6-associated neurodegeneration (PLAN), a spectrum of neurodegenerative conditions including infantile, childhood, and adult-onset forms. Thirty North African (26 Tunisian, 3 Algerian and one Libyan) patients with a clinical suspicion of infantile-onset PLAN underwent clinical, biological, neuro-physiological, and neuroimaging examinations and PLA2G6 sequencing. Twenty-nine children had the commonest form of infantile-onset PLAN, with early onset of psychomotor regression, hypotonia, pyramidal and cerebellar signs, and abnormal ocular movements. The phenotype was highly homogeneous, with rapid development of severe spastic tetraparesis, cognitive impairment, and optic atrophy. Twenty-eight patients underwent routine biochemical testing. All patients showed mildly increased levels of aspartate aminotransferase and lactate dehydrogenase even at early stages of the disease. Neuroimaging showed cerebellar atrophy and claval hypertrophy to be the commonest and earliest signs, while cerebellar cortex hyperintensity and pallidal iron deposition were later findings. Motor or sensory motor axonal neuropathy was frequent (20 of 29). Fifteen patients from 10 families shared the same mutation (p.V691del). One patient fitted the diagnosis of the much rarer childhood-onset PLAN. Despite the early onset (18 months), clinical progression was slower, with behavioral disturbances and dystonia. This patient carried a missense variant predicted to be less deleterious. The PLAN-associated phenotypes are delineated and a common North African founder mutation is identified. Elevated AST/ALT ratio associated to high LDH values could be considered a potential supportive biomarker to point toward the diagnosis of PLAN even in the very early stages of the disease.

If we are to see an increase in the development of treatments for lysosomal storage diseases such as mucopolysaccharidosis (MPS) and mucoliposis (ML; caused by the body’s inability to produce specific enzymes), we need to find the patients so that we can bring them to the attention of pharmaceutical and biotechnology companies. Individually, these rare diseases have very small patient populations and perhaps would be difficult to justify individual registries for each. The National MPS Society joined 22 MPS advocacy organizations and AltaVoice to develop a registry which can be used to collect and analyze information on MPS and ML patients as part of the AltaVoice|Invitae CONNECT website (https://goo.gl/jbv1oi). Providing patients and families with an outlet to find pertinent information pertaining to MPS and ML diseases, such as where Natural History Studies and clinical trials are taking place, or making themselves known by participating in a centralized registry is essential. It will also bring families from around the world closer together and give them access to information that they may not have available otherwise. We will describe how the registry works and the types of data collected which may help to decrease patient burden by not doing multiple surveys. In addition, the Registry has been translated into Spanish and Portuguese, with more languages to come. This is an example of a patient registry managed by patient groups for patients which we feel is optimal as we have the reach into patient communities that pharmaceutical companies do not. We will also illustrate how close collaborations between parent/patient-led disease organizations and clinical and company researchers is essential to ensure our limited funding and time is well spent as we try to identify treatments. The data offer researchers and medical professionals insights on what it means to live with these diseases and to find patients for treatments, research studies, clinical trials, and posttreatment programs. Any person diagnosed with MPS and ML can register with ConnectMPS.org.

LBN 20 - ConnectMPS Registry Project: Connecting Mucopolysaccharidosis and Mucolipidosis Patients

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If we are to see an increase in the development of treatments for lysosomal storage diseases such as mucopolysaccharidosis (MPS) and mucoliposis (ML; caused by the body’s inability to produce specific enzymes), we need to find the patients so that we can bring them to the attention of pharmaceutical and biotechnology companies. Individually, these rare diseases have very small patient populations and perhaps would be difficult to justify individual registries for each. The National MPS Society joined 22 MPS advocacy organizations and AltaVoice to develop a registry which can be used to collect and analyze information on MPS and ML patients as part of the AltaVoice|Invitae CONNECT website (https://goo.gl/jbv1oi). Providing patients and families with an outlet to find pertinent information pertaining to MPS and ML diseases, such as where Natural History Studies and clinical trials are taking place, or making themselves known by participating in a centralized registry is essential. It will also bring families from around the world closer together and give them access to information that they may not have available otherwise. We will describe how the registry works and the types of data collected which may help to decrease patient burden by not doing multiple surveys. In addition, the Registry has been translated into Spanish and Portuguese, with more languages to come. This is an example of a patient registry managed by patient groups for patients which we feel is optimal as we have the reach into patient communities that pharmaceutical companies do not. We will also illustrate how close collaborations between parent/patient-led disease organizations and clinical and company researchers is essential to ensure our limited funding and time is well spent as we try to identify treatments. The data offer researchers and medical professionals insights on what it means to live with these diseases and to find patients for treatments, research studies, clinical trials, and posttreatment programs. Any person diagnosed with MPS and ML can register with ConnectMPS.org.

LBN 21 - Exhaustive Analysis of BH4 and Dopamine Biosynthesis Genes in Patients With Dopa-Responsive Dystonia

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Dopa-responsive dystonia is a childhood-onset dystonic disorder, characterized by a dramatic response to low dose of l-Dopa. Dopa-responsive dystonia is mostly caused by autosomal dominant mutations in the GCH1 gene (GTP cyclohydrolase1) and more rarely by autosomal recessive mutations in the TH (tyrosine hydroxylase) or SPR (sepiapterin reductase) genes. In addition, mutations in the PARK2 gene (parkin) which causes autosomal recessive juvenile parkinsonism may present as Dopa-responsive dystonia. In order to evaluate the relative frequency of the mutations in these genes, but also in the genes involved in the biosynthesis and
recycling of BH4, and to evaluate the associated clinical spectrum, we have studied a large series of index patients (n = 64) with dopa-responsive dystonia, in whom dystonia improved by at least 50% after l-dopa treatment. Fifty-seven of these patients were classified as pure dopa-responsive dystonia and 7 as dopa-responsive dystonia-plus syndromes. All patients were screened for point mutations and large rearrangements in the GCH1 gene, followed by sequencing of the TH and SPR genes, then PTS (pyruvoyl tetrahydropterin synthase), PCBD (pterin-4a-carbinolamine dehydratase), QDPR (dihydropteridin reductase), and PARK2 (parkin) genes. We identified 34 different heterozygous point mutations in 40 patients and 6 different large deletions in 7 patients in the GCH1 gene. Except for one patient with mental retardation and a large deletion of 2.3 Mb encompassing 10 genes, all patients had stereotyped clinical features, characterized by pure dopa-responsive dystonia with onset in the lower limbs and an excellent response to low doses of l-dopa. Dystonia started in the first decade of life in 40 (85%) patients and before the age of 1 year in 1 (2.2%) patient. Three of the 17 negative GCH1 patients had mutations in the TH gene, 2 in the SPR gene and 1 in the PARK2 gene. No mutations in the 3 genes involved in the biosynthesis and recycling of BH4 were identified.

LBN 22 - Newborn Screening for 6 Lysosomal Storage Disorders in a Cohort of Mexican Health System: Follow-Up of 5-Year Findings

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To evaluate the results of a lysosomal newborn screening (NBS) program in a cohort of 35 000 Mexican patients over the course of 5 years in a closed Mexican Health System (Petroleos Mexicanos Health services). Study Design: Using dried blood spots (DBS), we performed a multiplex tandem mass spectrometry enzymatic assay for 6 lysosomal storage disorders (LSDs) including Pompe disease, Fabry disease, Gaucher disease, MPS I, Niemann-Pick type A/B, and Krabbe disease. Screen-positive cases were confirmed using leukocytes enzymatic activity and DNA molecular analysis. Results: From August 2012 to June 2017, 35 000 patients were screened and 31 patients were confirmed to have an LSD phenotype. Final distributions include 12 Pompe disease, 7 Fabry disease, 3 MPS I, 4 Niemann-Pick type A/B patients, 2 Krabbe patients, and 1 Gaucher patient. We discuss the follow-up and early treatment of these patients. Discussion: NBS is a major public health achievement that has decreased the morbidity and mortality of inborn errors of metabolism. The introduction of NBS for LSDs presents new challenges. This is the first multiplex Latin American study of 6 LSDs detected through NBS.

LBN 23 - Genetic Diagnosis of Metabolic Disorders via RNA Sequencing

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Across a variety of metabolic disorders, half of the patients do not receive a diagnosis by whole exome sequencing (WES). We reasoned that the inconclusive WES can be attributed to the incomplete capture of variants, especially noncoding variants, or the failure to prioritize them. Whereas the former can be overcome by whole genome sequencing (WGS), the vast number of variants generated by WGS and poor understanding of the noncoding genome obscure prioritization. RNA sequencing (RNA-sequ), in turn, might ease the prioritization of variants by unravelling their effects on RNA abundance and sequence. We performed RNA-sequ on 105 fibroblast cell lines from patients with a suspected metabolic disorder including 48 patients for which WES was inconclusive. We systematically prioritized genes (i) with aberrant expression level, (ii) with aberrant splicing, and (iii) monoallelic expression of rare variants to estimate their disease association. The analysis identified per sample on average 6 monoallelic expressed variants, 1 expression outliers, and about 5 splice defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. This small number of events allowed manual inspection and validation. Follow-up studies in 2 patients with RCCI defects. 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validation of strong candidates in additional samples is ongoing. In recent years, WES has become the gold standard for molecular diagnosis. However, a substantial amount of patients remains without diagnosis after WES. To bridge this diagnostic gap, we successfully applied RNA sequencing in combination with bioinformatics filtering criteria. Importantly, this approach is applicable for any rare disease setting and allows the discovery of new disease-associated gene. We therefore predict that RNA sequencing will become an essential companion of genome sequencing.

**LBN 24 - First Case of Sanfilippo Syndrome Type A (MPS III A) Diagnosed in the State of Ceará, Brazil**

Maria Denise Carvalho de Andrade, Ellaine Dória Fernandes Carvalho, Krishnamurti de Moraes Carvalho, Isabella Fernandes Carvalho, and Roberto Giugliani

The mucopolysaccharidoses (MPS) comprise a group of inherited diseases caused by the deficiency of lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs), formerly called mucopolysaccharides. Mucopolysaccharidosis type III (MPS III or Sanfilippo Syndrome) is a lysosomal disease caused by deficiency in one of the 4 enzymes involved in the degradation of heparan sulfate (HS). Each of the 4 subtypes (A, B, C, and D) is caused by the deficiency of a specific enzyme. Subtype A is caused by deficiency of the enzyme heparan-N-sulphatase (sulphamidase). We report a 9-year-old female infant who is the first child of a consanguineous and healthy couple. Prenatal was uneventful. At 2 years of age, she lost the ability to walk and convulsions episodes begun when she was 5 years old. Physical examination at 5 years old disclosed coarse facies, hirsutism, and hepatosplenomegaly. At this time, she was already using anticonvulsants. The echocardiogram was normal, while the X-ray of the spine showed discrete scoliosis of the thoracolumbar axis and small elevation in the left iliac crest in relation to the right. The cranial MRI revealed marked enlargement of the supratentorial cerebral ventricles, diffuse accentuation of cortical grooves, cisterns and cerebral fissures, retrocerebellar cystic formation in communication with the fourth ventricle, suggestive of Dandy Walker. The molecular analysis was performed, and it was detected the variation p.Gly80Val in homozygosis. This result confirmed that the patient is affected by the Sanfilippo type A disease (MPS III A), being the first case of this condition diagnosed in Ceará state, Brazil.

**LBN 25 - NV1205 for the Treatment for X-Linked Adrenoleukodystrophy (X-ALD)**

Masoud Mokhtarani, Giovanni Ferrara, and Thomas Scanlan

X-ALD is a genetic disease due to mutation of the ABCD1 gene on the X-chromosome with a worldwide incidence of 1:17 000. ABCD1 encodes a peroxisomal membrane protein that facilitates transport and degradation of very long chain fatty acids (VLCFA) in the peroxisome. ABCD1 mutations result in an inability to degrade VLCFA. VLCFA accumulates in all tissues, and accumulation in the neuronal white matter and adrenal cortex leads to Addison disease and varying degrees of neurological symptoms. Approximately 40% of affected young males develop a cerebral form of the disease, or childhood cerebral ALD (CCALD), characterized by cerebral inflammation, rapidly developing white matter lesions, severe neurological symptoms, vegetative state, and death in a few years. Adrenomyeloneuropathy (AMN) is the adult form of the disease manifested by spinal cord axonopathy leading to slowly progressive neurological symptoms such as paraparesis, gait disturbances, and fecal and urinary incontinence. The only available treatment for CCALD is hematopoietic stem cell transplant that must be performed early in the course of the disease to be effective. There is no therapy available for AMN. ABCD2, a gene encoding a homologous peroxisomal transporter to ABCD1, is an attractive therapeutic target with the possibility of correcting the underlying biochemical defect with potential disease-modifying properties. NV1205 is an orally bioavailable small molecule that upregulates the ABCD2 gene. Pharmacological studies in ABCD1 knockout mice treated with NV1205 have shown that long-term systemic administration of NV1205 results in VLCFA reductions in the central nervous system, adrenal cortex, and blood. The results support the upregulation of ABCD2 by NV1205 to complement the genetic defect as a treatment modality for all phenotypes of X-ALD.

**LBN 026 - The Comparison of the Digestion and Absorption of Trioctanoin (C8) and Triheptanoin (C7) in Patients With Long-Chain Fatty Acid Oxidation Disorders**

Melanie Gillingham, Kayla Guillory, Julie Martin, Dietrich Matern, Cary O. Harding, and Jerry Vockley

To determine if there is a difference in the appearance of triheptanoin or trioctanoin in peripheral circulation after a mixed
meal or a single nutrient bolus. This is a secondary analysis of Phase 2 Study of Triheptanoin to treat long-chain fatty acid oxidation disorders. Subjects with CPT2, VLCAD, or LCHAD/TFP were randomly assigned to consume triheptanoin or triheptanoin in a mixed breakfast meal. Blood was drawn fasting, 1, 2, and 4 hours after the meal. Separately, samples were drawn 20 minutes after an oral bolus of oil alone at 0.3 mg/kg lean body mass and again after 45 minutes of exercise. Blood samples were analyzed for free fatty acids, quantitative total fatty acid profiles, triglycerides, and apolipoprotein B48 (apoB48). There were 15 subjects per group. Serum free fatty acid concentrations were higher at fasting, decreased after feeding, and increased with exercise as expected. After the mixed meal, we observed a gradual rise in C8 (in subjects receiving C8) and C7 (in subjects receiving C7) in the quantitative fatty acid profile and both peaked at 4 hours. However, the total amount of C7 (104 ± 25 μmol/L) measured in plasma at 4 hours after a mixed meal was less than that of C8 (177 ± 88 μmol/L), after comparable intakes. The rise in plasma C8 and C7 corresponded with increased triglycerides and apoB48, suggesting that some of the C8 or C7 oil consumed had been incorporated into chylomicrons. Total plasma C7 (166 ± 37 μmol/L) or C8 (343 ± 191 μmol/L) concentrations were higher after the single nutrient oral bolus than after the mixed meal; triglycerides did not increase after the single nutrient bolus suggesting that C7 and C8 had been absorbed via the portal circulation. We expected C8 and C7 fatty acids to be absorbed in portal circulation and to peak in peripheral blood at 1 hour. However, both C8 and C7 peaked at 4 hours, suggesting that they may have been incorporated into chylomicrons after a mixed meal that also contained long-chain fat. The greater rise that they may have been incorporated into chylomicrons after a 1 hour. However, both C8 and C7 peaked at 4 hours, suggesting that they may have been incorporated into chylomicrons after a mixed meal that also contained long-chain fat. The greater rise in C8 plasma levels was also unexpected, suggesting there is a difference in the digestion, absorption, or clearance of C8 and C7. Both fatty acids rose after the single nutrient oral bolus and peaked at the final blood sample following exercise suggesting a more rapid rise in circulating C8 or C7 after a single nutrient bolus. The appearance of C8 or C7 in peripheral circulation differs when the oil is fed as a mixed meal versus a single nutrient bolus.

LBN 27 - Pilot Program of the Neonatal Screening Program in Guatemala

Nancy Gabriela Escobar Mena1, Bremily Chinchilla2, Miguel Angel Soto2, Raúl Velasco3, Nely Marroquin1, Mariana Herrera1, Claudia Osorio1, Nancy Zamora1, Luis Rosales1, Mariela Guerra1, Andrea Czollner4, Claudia Rangel1, Gretel Lemus3, Luis Alvarez1, and Claudia Carranza5

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Since 2015, the Institute for Scientific Research and Education on Human Genetic and Metabolic Diseases—INVEGEM—has been conducting a neonatal screening program in national hospitals in Guatemala City and in the rest of the country. Guatemala is one of fewest countries that does not have a national newborn screening program. Because of this, INVEGEM started an initiative of a pilot program to convinced the national authorities about the necessity of the development this program to all the newly born. The main objective of this program was to establish the frequencies of the major screened diseases performed around the world, these are congenital hypothyroidism, galactosemia, congenital adrenal hyperplasia, phenylketonuria, and cystic fibrosis. The importance of determining the frequency of each disease is that in Guatemala, there are no data reported previously. Guatemala is a multiethnic country, so the frequency of these diseases could be different from the reported in other countries. Until May 2017, 13,132 neonatal screening tests had been performed. To the date, 3 children with congenital hypothyroidism (1 in 2921), 6 with congenital adrenal hyperplasia (1 in 1993), 1 with galactosemia (1 in 8781), and 1 with cystic fibrosis (1 in 8716) have been detected and confirmed. Based on an extended screening performed on 237 newborns, 1 had furthermore been detected with maple syrup disease, 1 with hemoglobinopathies, 1 with methylmalonic acidemia, 1 with severe combined immunodeficiency, and 2 with partial deficiency of biotinidase. Those patients were treated accordingly as soon as possible to avoid irreversible damage such as mental retardation or even death. In conclusion, in Guatemala, during the 2 years of the program, the most frequent diseases founded are congenital adrenal hyperplasia and congenital hypothyroidism; while no case of phenylketonuria has been confirmed until now. These data are still few, to established definitive frequencies, so we reported here partial results about the positive screening that we have evaluated.


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Gaucher disease is the most common form of hereditary enzy-mopathies in the group of lysosomal diseases. This disease is autosomal recessive and is characterized by a deficiency of the enzyme β-glucosidase, which is clinically manifested by hepatic and splenomegaly, cytopenia, osteopathies, and sometimes involvement of the nervous system. The degree of clinical manifestations varies considerably, and although some geno-types are often associated with mild or severe symptoms, a
certain correlation between the genotype and the phenotype has not yet been studied sufficiently. Although 93% of the mutant alleles in Ashkenazi Jewish type 1 patients were N370S, c.848insG, IVS2+1G→A or L444P, these 4 mutations accounted for only 49% of mutant alleles in the non-Jewish type 1 patients. We reported a case of a 13-year-old child with type I Gaucher. First symptoms were visible in the first year of life in the form of an enlarged abdomen. Further, symptoms were spleen enlargement +9 to 10 cm, liver enlargement +3 to 4 cm, hemorrhagic rash, anemia, and thrombocytopenia. The diagnosis of Gaucher was established when he was 1 year 9 months old. GD was confirmed in the Metabolic Center of National Children’s Hospital OHMATDET by undetectable β-glucosidase activity. Full gene analysis demonstrated homozygous mutation G377S/G377S. From the age of 2 years 11 months, patient received an enzyme replacement therapy (Cerezyme—recombinant glucocerebrosidase) at a dose of 60 IU/kg biweekly. Within 4 years, the child received therapy regularly, which led to positive dynamics of the general condition and a significant improvement in hematological parameters. Diminished liver size to age, and the size of spleen reduced by 1/3. Clinically, there was no hemorrhagic rash. Due to family reasons and problems in compliance from age 8 to 12, patient did not perform replacement therapy regularly, which led to a deterioration of the clinical picture and laboratory indicators. Last year, despite regular administration in the age-related dosage, the size of the spleen remained large, and calcifications appeared. Now the patient is 13 years and changes in behavior are seen: he hardly talks and shows autistic features. The G377S mutation is rare and usually seen in Portuguese and Spanish descent Gaucher type I patients and is also seen in type 3 GD (neuropathic GD). These findings and our case indicate that G377S cannot be classified as mild and suggest an allele-dose effect for this mutation.

LBN 29 - Leigh Syndrome in a Neonate

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Leigh syndrome is characterized by subacute necrotizing encephalomyelopathy as a result of both nuclear and mitochondrial mutations. The disease generally presents between 3 months and 2 years, though here we report a case of acute and severe neonatal onset. A 19-day-old female newborn was brought to the emergency room in the setting of a week of poor feeding and worsening lethargy. She was born at term with a birth weight of 3.43 kg. She was found to be hypothermic (30.8°), bradycardic, somnolent, with poor respiratory effort, apneas, and an associated respiratory acidosis (pH 7.21, PCO2 83). Examination was notable for profound hypotonia and hyporeflexia. She had frequent multifocal electrographic-only seizures. Serum and cerebrospinal fluid lactate were elevated at 4.7 and 9.8 mmol/L, respectively (normal <2.2 and 2.8). Magnetic resonance imaging of the brain showed restricted diffusion within both cerebral hemispheres, the entire corpus callosum, deep gray nuclei, brain stem, and uppermost cervical cord. There was an elevated lactate peak in the basal ganglia on spectroscopy. Mitochondrial DNA analysis revealed a homoplasmic pathogenic variant (T10158C mutation, serine to proline) in the MT-ND3 gene, a subunit of the respiratory chain complex I. Her unaffected mother did not have the mutation in her blood. The patient ultimately died 1 month after disease onset. This case is notable for the unusually early age of onset and severity of Leigh syndrome. It serves as an important reminder to consider a mitochondrial disorder as an etiology for neonatal neurologic decompensation in addition to other more common disorders like sepsis, hypoxic ischemic injury, stroke, or other inborn errors of metabolism.

LBN 30 - c-Abl Mediates Tyrosine TFEB Phosphorylation and Its Cytoplasmic Localization: Implications in the NPC Cholesterol Lysosomal Storage Disease

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The transcription factor EB (TFEB) is the master regulator of the lysosomes biogenesis and function and the autophagy pathway. The activity and translocation to the nucleus of TFEB depends on its phosphorylation state. The inhibition of the proapoptotic tyrosine kinase c-Abl increases Lamp1 protein levels and autophagy flux. The aim of this work was to analyze if c-Abl inhibition promotes TFEB nuclear translocation and as consequence ameliorates cholesterol accumulation in the lysosomal storage disease Niemann-Pick type C (NPC). We modulated c-Abl using a siRNA and different c-Abl inhibitors and followed TFEB-GFP subcellular localization. Also, we evaluated the TFEB tyrosine phosphorylation status by immunoprecipitation and phospho-Tyr Western blot in cells overexpressing c-Abl. In addition, we evaluated cholesterol accumulation by filipin staining in NPC mice and cells (NPC1 null fibroblasts and Hepa 1-6 and HT22 cells treated with the U18666A drug [U18]) treated with the c-Abl inhibitors. To directly evaluate the participation of c-Abl, we used c-Abl−/− U18-treated hippocampal neurons. TFEB is phosphorylated by c-Abl in tyrosine. Also, c-Abl inhibition induces TFEB nuclear translocation. In addition, c-Abl inhibitors reduced cholesterol accumulation in NPC cell models and mice. In c-Abl−/− neurons treated with U18, we observed increased Lamp1 protein levels and reduction in cholesterol accumulation. Our data strongly suggest that TFEB tyrosine phosphorylation by c-Abl impacts TFEB nuclear translocation, suggesting a novel signaling pathway involving these 2 proteins. Probably this signaling would modulate cholesterol homeostasis in NPC disease. Supported by Fondecyt 1161065 (AA) and 1150186 (SZ), Fondef D10I1077, CARE-Chile-UC PFB 12/2007, and CONICYT CHILE.
LBN 31 - The FIND Project: Results of Selective Screening Based on Clinical Symptoms for Early Detection of Mucopolysaccharidoses

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One of the main problems in lysosomal diseases is the diagnosis delay due to their multisystem presentation causing pediatricians to treat different signs and symptoms in isolation. We present our 3-year experience in the early detection of mucopolysaccharidoses based on symptoms. We performed a nationwide program on risk pediatric population (0-18 years), based on clinical criteria. With the help of scientific meetings and pharmaceutical industry, we distributed kits with the necessary material: informed consent, clinical guide with the necessary material: informed consent, clinical guide with the symptoms and warning signs to be considered, and the analytical paper Whatman 903 to collect biological samples of urine and blood. From July 1, 2014, to June 30, 2017, a total of 692 kits from all over Spain have been requested to our center. We received a total of 366 patients from 49 different provinces of the 50 that exist in Spain (18% from primary care and 82% from hospitals). In all of them, we determined the urine levels of creatinine and glycosaminoglycans (GAG) as main screening method. The GAG levels exceeded the cutoff for his age in 15% of samples. We confirm high GAG levels in 24 after requesting a second sample. Of the 24 cases, we have identified a total of 17 cases of MPS (3 MPSI, 2 MPSII, 4 MPSIIIA, 2 MPSIIIB, 4 MPSIVA and 2 MPSVI). All of them showed enzymatic activities below the reference value and 76% of cases were below 5 years old. GAG determination in an impregnated paper urine sample has shown to be a rapid, simple, and reliable screening for MPS that can open the gate to be performed as newborn screening.

LBN 32 - A Rare SNP in the Placental Riboflavin Transporter Gene Causes Transient Multiple Acyl-CoA Dehydrogenation Deficiency, Detectable by Newborn Screening

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Multiple acyl-CoA dehydrogenation deficiency (MADD) is a rare inborn error of metabolism, which may have a favorable outcome when treated with high doses of riboflavin. MADD is most often caused by recessive mutations in genes coding for the electron transfer flavoprotein and its dehydrogenase, which link mitochondrial FAD-containing acyl-CoA dehydrogenase reactions to ATP production in the respiratory chain. More recently, MADD has been linked to mutations in genes involved in cellular riboflavin transport or in the synthesis of the FAD cofactor from riboflavin. Fetal riboflavin status is largely dependent on the availability of riboflavin in maternal circulation and placental transport of riboflavin. Thus, maternal riboflavin deficiency and/or gene defects in placental riboflavin transport can potentially cause transient MADD and significant disease in the newborn child. So far, a single case of transient MADD has been reported in a child to a mother carrying a heterozygous deletion of the SLC52A1 gene, responsible for placental riboflavin transport. We here report another case of transient MADD, caused by a rare single-nucleotide polymorphism (SNP) in SLC52A1. The newborn girl presented in the first few days of life with hypotonia, lethargy, and metabolic lactic acidosis. Newborn screening filter card analysis revealed elevation of multiple acyl-carnitines (C6-C14), resembling MADD profile. The MADD biochemistry was confirmed by analysis of plasma acylcarnitines and urine organic acids. Riboflavin treatment corrected the MADD biochemistry and clinical symptoms. Analysis of the mother’s riboflavin status showed that she was borderline riboflavin deficient. Sequencing of MADD candidate genes revealed that the mother and her child were carriers of a c.1134+11G>A mutation in SLC52A1. Using splicing reporter minigenes and RNA affinity purification of nuclear splice proteins, we show that the mutation creates a binding site for the splice inhibitory hnRNP A1 protein and causes exon 4 skipping. The c.1134+11G>A mutation has a minor allele frequency of 0.2% (ExAc Server) in the general population and could be a risk factor for the development of transient MADD and significant illness in children to pregnant mothers with subclinical riboflavin deficiency. Newborn screening programs should be aware of this MADD-associated SNP.

LBN 33 - Epidemiology of Mucopolysaccharidoses

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Multiple acyl-CoA dehydrogenation deficiency (MADD) is a rare inborn error of metabolism, which may have a favorable outcome when treated with high doses of riboflavin. MADD is most often caused by recessive mutations in genes coding for the electron transfer flavoprotein and its dehydrogenase, which link mitochondrial FAD-containing acyl-CoA dehydrogenase reactions to ATP production in the respiratory chain. More recently, MADD has been linked to mutations in genes involved in cellular riboflavin transport or in the synthesis of the FAD cofactor from riboflavin. Fetal riboflavin status is largely dependent on the availability of riboflavin in maternal circulation and placental transport of riboflavin. Thus, maternal riboflavin deficiency and/or gene defects in placental riboflavin transport can potentially cause transient MADD and significant disease in the newborn child. So far, a single case of transient MADD has been reported in a child to a mother carrying a heterozygous deletion of the SLC52A1 gene, responsible for placental riboflavin transport. We here report another case of transient MADD, caused by a rare single-nucleotide polymorphism (SNP) in SLC52A1. The newborn girl presented in the first few days of life with hypotonia, lethargy, and metabolic lactic acidosis. Newborn screening filter card analysis revealed elevation of multiple acyl-carnitines (C6-C14), resembling MADD profile. The MADD biochemistry was confirmed by analysis of plasma acylcarnitines and urine organic acids. Riboflavin treatment corrected the MADD biochemistry and clinical symptoms. Analysis of the mother’s riboflavin status showed that she was borderline riboflavin deficient. Sequencing of MADD candidate genes revealed that the mother and her child were carriers of a c.1134+11G>A mutation in SLC52A1. Using splicing reporter minigenes and RNA affinity purification of nuclear splice proteins, we show that the mutation creates a binding site for the splice inhibitory hnRNP A1 protein and causes exon 4 skipping. The c.1134+11G>A mutation has a minor allele frequency of 0.2% (ExAc Server) in the general population and could be a risk factor for the development of transient MADD and significant illness in children to pregnant mothers with subclinical riboflavin deficiency. Newborn screening programs should be aware of this MADD-associated SNP.
The aim of this study was to obtain data about the epidemiology of the different types of mucopolysaccharidoses in Japan and Switzerland and to compare with similar data from 21 other countries reported. This is the first worldwide epidemiology for MPS. Data for Japan were collected between 1982 and 2009, and 467 cases with MPS were identified. The combined birth prevalence was 1.53 per 100 000 live births. The highest birth prevalence was 0.84 for MPS II, accounting for 55% of all MPS. MPS I, III, and IV accounted for 15%, 16%, and 10%, respectively. MPS VI and VII were more rare and accounted for 1.7% and 1.3%, respectively. A retrospective epidemiological data collection was performed in Switzerland between 1975 and 2008 (34 years), and 41 living MPS patients were identified. The combined birth prevalence was 1.56 per 100 000 live births. The highest birth prevalence was 0.46 for MPS II, accounting for 29% of all MPS. MPS I, III, and IV accounted for 12%, 24%, and 24%, respectively. As seen in the Japanese population, MPS VI and VII were more rare and accounted for 7.3% and 2.4%, respectively. The high birth prevalence of MPS II in Japan was comparable to that seen in other East Asian countries where this MPS accounted for approximately 50% of all forms of MPS. Birth prevalence was also similar in some European countries (Germany, Northern Ireland, Portugal, and the Netherlands), although the prevalence of other forms of MPS is also reported to be higher in these countries. Birth prevalence of MPS II in Switzerland and other European countries is comparatively lower. The birth prevalence of MPS III and IV in Switzerland is higher than in Japan but comparable to that in most other European countries. Moreover, the birth prevalence of MPS VI and VII was very low in both Switzerland and Japan. Overall, the frequency of MPS varies for each population due to differences in ethnic backgrounds and/or founder effects that affect the birth prevalence of each type of MPS, as seen for other rare genetic diseases. Methods for identification of MPS patients are not uniform across all countries, and consequently, if patients are not identified, recorded prevalence rates will be aberrantly low.

LBN 34 - Novel Surgical Reconstruction Rescues Life-Threatening Severe Tracheal Obstruction in Mucopolysaccharidoses

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Patients with severe tracheal obstruction in mucopolysaccharidoses (MPS), especially MPS IVA, are at risk of dying of sleep apnea and related complications. Two-thirds of patients with MPS IVA die of respiratory problem. Tracheal obstruction also leads to life-threatening complications during anesthesia as a result of the difficulty in managing the upper airway due to factors inherent to MPS, compounded by the difficulty in intubating and extubating the trachea. Although tracheostomy can address severe upper airway obstruction, lower airway obstruction, commonly associated with a narrow thoracic inlet and vascular compression, requires an alternative approach. Our goal is to provide the guidelines in the management of these patients that allow earlier recognition and intervention of tracheal obstruction. We present a series of cases with significant tracheal obstruction who were unrecognized due to the difficulty in interpreting tracheal narrowing airway symptoms. Sagittal MRI images of the cervical spine of 28 Morquio A patients (12 ± 8.14 years) showed that 19 (67.9%) of 28 patients had at least 25% tracheal narrowing and that narrowing worsened with age (all 8 patients over 15 years had greater than 50% narrowing). Eight (75%) of 28 patients were categorized as severe tracheal narrowing when images were evaluated in neutral head and neck position. The etiology of tracheal impingement by the brachiocephalic artery in Morquio A appears to be due to a combination of the narrow thoracic inlet crowding structures and the disproportionate growth of trachea and brachiocephalic artery in relationship to the chest cavity leading to tracheal tortuosity. We describe 6 cases with MPS IVA (4 cases were under ERT up to 5 years) whose near-fatal tracheal obstruction was relieved by timely surgical tracheal vascular reconstruction with dramatic resolution of respiratory symptoms, leading to marked improvements of ADL. Tracheal narrowing, often due to impression from the crossing tortuous brachiocephalic artery, increases with age in MPS IVA patients. Greater attention to the trachea is needed when evaluating cervical spine MRIs as well as other imaging and
clinical investigations, with the goal of establishing a timely treatment protocol to reduce the mortality rate in this patient population. This novel surgical procedure could be applicable to other types of MPS with severe tracheal obstruction.

**LBN 35 - c-Abl Signaling Is Activated and Relevant in Neuronal Models of Niemann-Pick Type A Disease**

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Niemann-Pick type A (NPA) disease is a fatal neurodegenerative disorder characterized by the deficiency in acid sphingomyelinase (ASM) and accumulation of sphingomyelin in lysosomes. Previously, our group described that the c-Abl/p73 pathway is activated and mediates the neurodegeneration in other storage diseases. Our aim was to evaluate the activation of the c-Abl signaling pathway and its participation in the neuronal pathology in NPA disease. We used the ASM deficient mouse and SHSY5Y neurons treated with desipramine as in vivo and in vitro NPA models, respectively. In NPA mice cerebellum, we evaluated Purkinje cell loss, inflammation, and the c-Abl/p73 pathway at different ages. In the NPA neuronal model, we evaluated c-Abl levels and viability. In addition, the effect of the c-Abl inhibitor imatinib on neurodegeneration and inflammation in NPA cerebellum and c-Abl/p73 signaling and neurons survival were evaluated in the in vivo and in vitro NPA models. The NPA mouse model presented progressive and early neurodegeneration in cerebellum accompanied with signs of inflammation and activation of c-Abl/p73 pathway starting 4 weeks of age. Accordingly, the cellular neuronal NPA model presented activation of this signaling. Interestingly, treatment with imatinib reduced neuronal death and caspase 3 active levels in the NPA neuronal model and preserved Purkinje neurons and reduced inflammation in the NPA cerebellum. The c-Abl pathway is activated and relevant in NPA neurodegeneration, supporting the potential use of imatinib for clinical treatment of NPA patients. FONDECYT: 1150186 (SZ) and 1161065 (AA) CARE-Chile-UC/PFB12/2007 and CONICYT-CH/Doctorado Nacional/2015-150038.

**LBN 36 - A Next-Generation Fabry Enzyme Replacement Therapy: Coformulation of a Proprietary Recombinant Human α-Galactosidase A With a Pharmacological Chaperone Has Greater Efficacy Than Agalsidase β in Mice**

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Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency in α-galactosidase A (α-Gal A) activity, leading to progressive accumulation of lysosomal globotriaosylceramide (GL-3) in multiple tissues. While enzyme replacement therapy (ERT) with recombinant human α-Gal A (rhα-Gal A), namely, agalsidase beta and agalsidase alfa, has brought many therapeutic benefits to patients, the infused enzymes tend to have low physical stability, short circulating half-lives in blood, and variable uptake into different disease-relevant tissues, all of which can impact efficacy and tolerability. We have developed a proprietary rhα-Gal A, ATB101, that is coformulated with the pharmacological chaperone AT1001 (1-deoxynojirimycin, migalastat hydrochloride). In vitro, AT1001 binds to ATB101, stabilizing the enzyme in an active conformation. When ATB101 was administered intravenously alone at 3 different doses to Gla knockout (KO) mice, dose-dependent, nonlinear pharmacokinetics were observed. Upon AT1001 coformulation (designated as ATB101/AT1001), the circulating half-life of ATB101 increased up to 2.3-fold, and the levels of active enzyme in disease-relevant tissues increased up to 2.7-fold, compared with enzyme alone. Importantly, in a repeat administration study in Gla KO mice, ATB101/AT1001 demonstrated greater enzyme potency for GL-3 reduction, with efficacy that reached or even exceeded that seen with a 10× dose of the standard of care (1 mg/kg agalsidase beta). Taken together, these data demonstrate the superior efficacy of ATB101/AT1001 over agalsidase beta in mice and suggest that ATB101/AT1001 coformulation may represent a next-generation ERT for Fabry disease warranting further investigation.

**LBN 37 - Saudi Newborn Screening Program Success and Challenges: Single-Center Experience**

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Newborn screening was started in 1962, and its history was full of successful stories and challenges. The development in the field of medical genetics has impacted on quality of newborn screening and outcomes. Saudi newborn screening was started in 2005, revealing an incidence of 1:1000. In this study, we are describing our experience with newborn screening over 2-year period. Retrospective review of newborn screening records at King Abdulaziz University Hospital (KAUH) between 2014 and 2015. All newborn born at KAUH were screened at 24 to 48 hours of age via dried blood spot using Tandem MS. Positive cases were repeated within 5 to 10 days. Newborn screening laboratory is located in another city where samples were shipped daily. According to national screening program, 16
disorders are included. Screening was performed according to local policy guided by national and international recommendations. Positive cases were followed and managed at the same center. Total of 6927 newborns were screened and revealing 50 positive case. Only 12% (6 cases) were true positive (phenylketonuria, VLCAD, citrullinemia, 3 MCC, propionic acidemia, and maple syrup urine disease) with incidence of 1:1154. Two cases presented before newborn screening result, case of propionic acidemia and citrullinemia, both had major squealy and one ended with mortality at 4 months of age. False-positive cases were mainly premature or asphyxiated newborns, and few with no risk factor identified. Newborn screening at KAUH revealed similar incidence to national statistics, which is 10 times higher than developed countries. Mild and late presenting disorders tend to benefit more from the screening. Limitation of newborn screening in early presenting conditions is still a problem. Prematurity and perinatal asphyxia were one of the risk factors for false-positive cases.

LBN 38 - Diagnosis and Monitoring of Patients With Glycoprotein Storage Disorders by Novel UPLC-MS/MS Oligosaccharide Analysis

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Majority of clinical laboratories utilize thin layer chromatography (TLC) to measure urinary free oligosaccharides (FOS) to identify patients with a variety of inborn errors of metabolism including the glycoprotein storage disorders, Pompe disease, and more recently several congenital disorders of glycosylation. However, TLC is not an optimal assay as it is not quantitative and lacks the sensitivity and specificity of a clinical diagnostic test. We developed a novel, rapid UPLC-MS/MS method to measure urinary FOS using reducing-end labeling. The relative concentration of 9 disease-specific oligosaccharides is determined by comparison to the peak area of a single internal standard. As an initial validation, we analyzed 51 urine samples from a patient cohort encompassing 8 LSDs: aspartylglucosaminuria (n = 3), beta-mannosidosis (n = 4), alpha-mannosidosis (n = 21), beta-mannosidosis (n = 1), beta-galactosidase deficiency (n = 8), Sandhoff disease (n = 2), sialidosis (n = 3), and galactosialidosis (n = 2), which were collected as part of the Glycoproteinoses Natural History Study or through routine diagnostic testing. Age-specific normal ranges were developed using 110 samples from unaffected controls. An increased abundance of the disease-specific oligosaccharide was identified in all 51 affected individuals. When compared to age-matched controls, the elevations ranged from 5- to 2100-fold, with fucosidosis (1285-fold), sialidosis (426-fold), galactosialidosis (265-fold), and aspartrylglucosaminuria (154-fold) showing the widest dynamic range. Urine samples from patients with alpha-mannosidosis, fucosidosis, and beta-mannosidosis post bone marrow transplantation had significantly lower oligosaccharide levels compared to untreated patients, indicating that this assay can be used to evaluate the efficacy of future treatments. We have also analyzed 80 urine samples from patients with mucolipidoses types II, II/III, or III and identified at least 1 FOS abnormality in all ML patients and were also capable of differentiating between MLII and MLIII patients. Identification of significant elevations in urinary FOS specific for Pompe disease (Glc4) and 2 types of congenital disorders of glycosylation suggest the assay can be used as a broad screen for an increasing number of inborn errors of metabolism. Based on the data accumulated so far, our assay is a significant improvement over TLC and is capable of avoiding false-positives due to dietary or medication-related metabolites.

LBN 39 - Glycogen Storage Disease Communication Platform: From Bedside to Home Site Monitoring

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Application of guidelines for individual patients with hepatic glycogen storage disease (GSD) are complicated by various issues, including geographic distances, heterogeneity between patients, a discrepancy between prescribed and used diets, and the fact that clinical (“bedside”) evaluation does not reflect the normal (“home site”) situation. The purpose of this project is to develop a teledmedicine platform to facilitate home site monitoring of individual patients with hepatic GSD. The GSD communication platform (GCP) is designed by ICT professionals, GSD patients, and health-care professionals, followed by a Conformité Européenne (CE) mark procedure. In phase 1, prototyping and software design of the GCP has occurred, consisting of 2 mobile web applications. The GSD App (for patients) and the GSD Clinical Dashboard (for health-care professionals) integrate (a) prescribed and registered diets, (b) data retrieval from continuous glucose monitor devices and activity wearables, (c) the newly developed hypoglycemia awareness module, (d) an automatically generated emergency protocol, and (e) communication tools. In phase 2, the software is developed by retrospective patient data entry. In phase 3, the software is implemented by a pilot prospective clinical entry of 12 GSD patients with GSD Ia (n = 3), GSD IIIa (n = 4) and GSD IX (n = 5). User evaluation is performed by system usability scale and open feedback. JIRA software issue tracker is used for managing the software development process. The GCP is the first telemedicine platform for an
inherited metabolic disease and can facilitate home site monitoring. In the future, the software may support second opinions, cross-border patient care, and research projects including clinical trials.

**LBN 40 - Development and Characterization of Patient-Specific iPSC-Derived Retinal Pigmentary Epithelia (RPE)–Like Cells as a Model of LCHAD-Associated Retinopathy**

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Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) is one of 3 enzymatic domains found within the trifunctional protein (TFP) complex that mediates long-chain fatty acid oxidation (FAO) in mitochondria. Unlike other FAO disorders, patients with LCHAD deficiency develop vision loss from progressive chorioretinopathy. Currently, there is no animal model available to study LCHAD-associated chorioretinopathy. While the mechanism of retinal pathogenesis in LCHAD deficient patients remains poorly understood, there is evidence to suggest that the initial physiologic perturbations begin in retinal pigment epithelial (RPE) cells and progress to other retinal cell layers. We sought to develop an in vitro RPE cell model as a tool to uncover pathogenic mechanisms caused by loss of LCHAD. In this study, we reprogrammed patient fibroblasts harboring the HADHA (G1528C) mutation into induced pluripotent stem cells (iPSC). These cells, along with wild-type control iPSCs, were subsequently differentiated into retinal pigment epithelium (RPE) through a directed method. Using immunofluorescence and RNA expression analysis, we have confirmed that iPSC-derived RPE are histologically similar to primary human RPE despite remaining homozygous for the G1528C mutation. Cellular energetics were evaluated in both wild-type and mutant RPE cells using the Seahorse Biosciences XF analyzer. Our results indicate that wild-type RPE exposed to 200 μM BSA-palmitate + carnitine in glucose-limited media show a steady increase in the oxygen consumption rate (OCR), a 1.5-fold increase over 45 minutes, when compared to cells treated with BSA alone. In contrast, LCHAD-deficient cells showed no change in OCR when exposed to palmitate, suggesting that their ability to utilize long-chain fatty acids as an energy source is impaired. LCHAD-deficient RPE that were fed BSA-palmitate (200 μM) + carnitine showed a dramatic increase in C16-OH acylcarnitine in the media after 48 hours (0.31 μM) compared to LCHAD-deficient RPE cells that were exposed to BSA alone (0.02 μM). Media collected from wild-type RPE under the same conditions showed no change either in the presence of palmitate (0.002 μM) or in the BSA control (0.002 μM). These results demonstrate that LCHAD-deficient RPE derived from patient iPSCs may be an effective model to study the pathophysiology of LCHAD-associated retinopathy and for the evaluation of potential novel therapies to treat this severely disabling disease.

**LBN 41 - Evolution of Pregnancy in a Patient With Classical Galactosemia**

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Galactosemia is a rare genetic disease, caused by a carbohydrate metabolism disorder (galactose), due to the deficiency of the galactose-1 phosphate-uridylytransferase enzyme. Gonadal toxicity appears to be limited to the ovary because galactosemic men do not show fertility abnormalities. Female patients with galactosemia are at high risk for premature ovarian failure. The risk of ovarian failure is a common concern, but spontaneous pregnancies, even on several occasions, may occur in young patients with galactosemia. Symptoms of this acute condition, caused by the accumulation of galactose and its metabolites, may regress under a galactose-free diet. To describe the evolution of pregnancy in a patient diagnosed with classic galactosemia. The nutritional status was evaluated using the body mass index at the beginning of pregnancy and in the 3 quarters comparing it with the reference values of the tables for Cuban pregnant women as well as the values of galactose in blood referring to the genetics laboratory. The restricted diet for the pathology was maintained, taking into account the caloric supplementation according to the quarterly evolution. The pregnancy was satisfactory, with adequate weight gain. Values of galactose in blood within normal parameters, coming to term without complications. With an adequate follow-up product of a strict diet, in a classic galactosemic patient, it is possible to achieve a satisfactory pregnancy.

**LBN 42 - Behavior of Galactosemia in Cuba in Different Stages for More Than 25 Years**

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Galactosemia as metabolic disease occurs in the world in approximately 1/50 000 births. The different enzymes involved totally or partially give rise to the diverse clinical manifestations. In Cuba, until the end of last century, diagnosis was made by clinical manifestations that sometimes accompanied the own disease complications. Currently, early diagnosis is possible by results obtained from newborn screening. To describe the behavior of galactosemia in Cuba, at different stages, for more than 25 years. A descriptive and retrospective study was carried out in 30 patients, of which 13 were diagnosed before newborn screening and 17 in a later stage, in the period from
March 1988 to March 2016. Weight and height measures were taken in every patient, comparing them with Cuban tables’ values, to determine their nutritional status at diagnosis and disease course. For those diagnosed prior the screening, the most important clinical manifestations, biochemical indicators at the disease onset and progression, including the dietary and therapeutic regimen to be followed after diagnosis were taken into account. For those diagnosed by the screening, breastfeeding was suppressed, indicating the dietary regimen to be followed, calling them periodically to specify their clinical, anthropometric, and biochemical progression. In those diagnosed prior the screening, the clinical manifestations were diarrhea 61.5%, lethargy and hypoglycemia crisis 15.4%, hepatic cholestasis 7.7%, cataracts 15.4%. Most of them (69.2%) had their nutritional status compromised due to diagnosis. By imposing the dietary and therapeutic regimen, a remarkable improvement in the clinical (100%), anthropometric (84.6%), and biochemical (100%) presentation was observed. Of those diagnosed by screening, most of them (95%) have a satisfactory clinical, anthropometric, and biochemical progression. Galactosemia in Cuba has behaved satisfactorily in different stages by timely diagnosis and periodic follow-up.

LBN 43 - Mouse Model of the Qatari R336C CBS Allele: Restoration of Enzyme Activity by Treatment With Proteasome Inhibitor

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Classical homocystinuria is a recessive inborn error of metabolism caused by mutations in the cystathionine beta-synthase (CBS) gene. The highest rates of CBS deficiency in the world are found in the country of Qatar. The estimated incidence of 1/1800 newborns is due to the combination of high rates of consanguinity and the presence of a founder mutation, c.1006C>T (p.R336C). This mutation does not respond to pyridoxine and is considered severe. Here, we describe the creation of a mouse that lacks the endogenous mouse Cbs gene and expresses human p.R336C CBS from a zinc-inducible transgene. Zinc-treated Tg-R336C Cbs−/− mice have a mean serum tHcy of 314 mM compared to 19.4 mM for mice expressing wild-type human CBS (Tg-hCBS Cbs−/−). They also show a 20-fold increase in liver tHcy compared to controls. Liver p.R336C mRNA levels are similar to those observed for wild-type hCBS, but steady-state protein levels are much lower, suggesting that the p.R336C alteration affects protein turnover. Measurement of CBS activity in liver lysates reveals that p.R336C has significant residual activity, about 9% of that observed in lysates from Tg-hCBS Cbs−/− mice. Treatment of Tg-R336C Cbs−/− mice with the proteasome inhibitor borretuzomib resulted in stabilization of liver CBS protein and an increase in activity to levels found in Tg-hCBS Cbs−/− mice. Surprisingly, serum tHcy did not fully correct to the levels seen in Tg-hCBS Cbs−/− mice. Kinetic studies on mouse liver extracts reveal that p.R336C reduces the binding affinity for the substrate serine by almost 7-fold and also has increased requirement for PLP in vitro, which could explain this discrepancy. These studies demonstrate that the p.R336C alteration effects protein stability and that proteasome inhibitors in combination with increased serine and pyridoxine may potentially be useful in the treatment of these patients.

LBN 44 - Optimization of Separation and Detection of O-Phthalaldehyde (OPA) Derivatives of Amino Acids Using Reversed-Phase Liquid Chromatography With Fluorescence Detection

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Measurement of amino acids by reverse-phase high-performance liquid chromatography techniques (RP-HPLC) is one of important tools for the diagnosis of inborn errors of metabolism. The aim of this study was to optimize chromatographic conditions for the determination of the plasma amino acids using reverse-phase high-performance liquid chromatography techniques (RP-HPLC) with precolumn derivatization by O-phthalaldehyde (OPA) in combination with 2-mercaptetoethanol. The optimization of chromatographic conditions includes the separation temperature, the injection volume, and the mobile phase flow rate. To obtain the best chromatographic conditions, the mobile phases were optimized to provide appropriate selectivity and sensitivity (elution mode [isocratic and gradient], the pH of the aqueous buffer). Standard mixture of 6 amino acids have been used (valine, arginine, leucine, isoleucine, tyrosine, and phenylalanine) with different concentrations. For the plasmatic samples, a deproteinization step with perchloric acid was performed. Optimal values of the HPLC-RP method were found: injection volume: 5 μL; mobile phase flow rate: 0.5 mL/min; column temperature: 22°C; detector settings: λex = 340 nm and λem = 455 nm. The optimum separation of these amino acids is performed in 30 minutes using a C18 column with a binary gradient containing phosphate buffer pH 7.8 and methanol as the mobile phase. A gradient RP-HPLC method was performed using mobile phase: A: phosphate buffer, B: methanol; Gradient (Time, %B): 0 to 12 minutes, 58%, 12 to 30 minutes, 100%. The results indicated a good chromatographic separation of amino acids by this method. The use of o-phthalaldehyde (OPA) derivative reagent...
increased the efficiency and resolution of amino acids chromatographic separation. The use of a gradient elution resulted in better sensitivity, improving the peak symmetry. Detection by fluorescence yields excellent sensitivity; it produces stable baselines during gradient elution. The proposed method using o-phthalaldehyde derivatives and RP-HPLC was applied successfully for the simultaneous separation of amino acids in plasmatic samples.

LBN 45 - Citrullinemia Type 2: A Good Reason to Consider Nutrition as a Therapeutic Intervention in Adult Neurology Practice

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Citrin deficiency is an inherited metabolic disease caused by mutations in SLC25A13 encoding mitochondrial transporter citrin and can manifest in different clinical pictures according to age, from neonatal intrahepatic cholestasis to citrullinemia type 2 (CTLN2) in adults. The typical food preference, aversion to carbohydrate-rich foods and fondness for protein and/or lipid-rich foods, is a self-protective mechanism seen in affected individuals. Introduction of high-carbohydrate containing conventional enteral/parenteral nutrition solutions used in neurointensive care units (NICU) may further worsen the encephalopathy in yet undiagnosed CTLN2 patients and prompt recognition of this nutrition-induced deterioration may be diagnostic and lifesaving for the critically ill patients. A 48-year-old previously healthy Turkish male was diagnosed to have citrin deficiency, after a 3-months lasting fluctuating encephalopathy period. Diffusion restricted high signal lesions seen in bilateral cingulate gyri, insular, and temporal cortices led to the suspicion of an inherited metabolic disease, after excluding infectious, paraneoplastic, autoimmune etiologies. Plasma amino acid analysis showed hypercitrullinemia (522 μmol/L) with normal plasma ammonia levels. With the suspicion of CTLN2, plasmapheresis was performed for 2 days and a diet low in carbohydrates high in protein and fat was introduced with l-arginine and sodium pyruvate supplementation. Mental status dramatically improved within 2 days and he was discharged with sequel. Homozygous pathogenic c.1706_1707delTA variant was found in SLC25A13 and family screening led us to diagnose 2 asymptomatic patients. The neurologists play a critical role in early recognition of rare but treatable metabolic encephalopathies like CTLN2. Plasma ammonia and amino acids should be added to the routine checklist in all acute-onset encephalopathies.

LBN 46 - Utility of Whole Exome Sequencing (WES) in the Diagnosis of Lysosomal Storage Disorders (LSDs)

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WES is the current test of choice for patients with complex phenotypes and previous uninformative genetic testing. Although LSDs are well-defined disorders, they have overlapping phenotypes, and despite biochemical analyses and NGS panels being available, clinicians might opt for WES analysis when unable to arrive at a specific diagnosis. The high cost and large time to diagnosis of stepwise single-gene testing or NGS panels, unavailability of enzyme analysis locally, and the possibility of expanding the analysis to a larger set of genes make WES a good option for patients with LSDs. In this study, we analyzed the reported WES cases to date with respect to 41 LSD genes, to determine if WES is a good diagnostic tool for LSD cases. The cases were then reviewed to identify those with a confirmed or possible diagnosis. On review, 107 cases had at least one reported variant (a pathogenic [PV], likely pathogenic [LPV], or variant of unknown significance [VUS]) in an LSD gene. Confirmed genetic diagnosis: In 53 out of 107 cases, a diagnosis was confirmed, as 49 cases were homozygous/compound heterozygous for a PV/LPV in an autosomal recessive (AR) gene, 1 case was hemizygous for an LPV in an X-linked (XL) gene and 3 cases were compound heterozygotes for a PV and a VUS. Possible genetic diagnosis (VUS): In 48 out of 107 cases, a diagnosis of LSD might be possible, as 41 cases were homozygous/compound heterozygous for a VUS in an AR gene and 7 cases were hemizygous for a VUS in an XL gene. Single variant, unconfirmed diagnosis, carrier status: In 13 cases, only 1 variant was detected in an AR gene. For 7 cases, deletion/duplication analysis was recommended due to significant overlap of patient symptoms with the disease. In 4 cases, the LSD variant was identified in an unaffected relative, segregated in the family and had significant overlap with the affected index’s symptoms. Two cases were incidental carriers of an LSD variant and had another diagnostic variant. Approximately 49.5% of cases had a confirmed diagnosis of LSD on WES. These results show that despite a distinct phenotype and availability of biochemical testing, many patients with LSDs remain
If we are to see an increase in the development of treatments for lysosomal storage diseases such as mucopolysaccharidosis (MPS) and mucoliposis (ML; caused by the body’s inability to produce specific enzymes), we need to find the patients so that we can bring them to the attention of pharmaceutical and biotechnology companies. Individually, these rare diseases have very small patient populations and perhaps would be difficult to justify individual registries for each. The National MPS Society teamed up with 22 MPS advocacy organizations and Avieta to develop a registry which can be used to collect and analyze information on MPS and ML patients as part of the Patient Crossroads CONNECT website (connectMPS.org). Providing patients and families with an outlet to find pertinent information pertaining to MPS and ML diseases, as where Natural History Studies and clinical trials are taking place, or making themselves known by participating in a centralized registry is essential. It will also bring families from around the world closer together and give them access to information that they may not have available otherwise. We will describe how the registry works and the types of data collected which may help to decrease patient burden by not doing multiple surveys. In addition, the Registry has been translated into Spanish and Portuguese, with more languages to come. This is an example of a patient registry managed by patient groups for patients which we feel is optimal as we have the reach into patient communities that pharmaceutical companies do not. We will also illustrate how close collaborations between parent/patient led disease organizations and clinical and company researchers is essential to ensure our limited funding and time is well spent as we try to identify treatments. The data offer researchers and medical professionals’ insights on what it means to live with these diseases and to find patients for treatments, research studies, clinical trials and posttreatment programs. Any person diagnosed with MPS and ML can register for ConnectMPS.

Background: Homocystinuria is a rare inborn error of methionine metabolism caused by cystathionine B synthase (CBS) deficiency. However, in Qatar, the prevalence is 1:1800 due to a founder Qatari missense mutation.1006C>T, in which arginine (R) is replaced with cysteine (C) at CBS p.336. Untreated homozygous patients are clinically severely affected with intellectual disability and multisystem complications.

Objectives: To repair the R336C-CBS deficient enzymatic activity by different approaches using 2 in vivo models: (i) Yeast (Saccharomyces cerevisiae) model: established by generating cbs/yeast strains express in trans, the wild-type (wt) human CBS (WY79p.hCBS strain), and the cbs-R336C (WY79p.R336C strain) and (ii) HEK293 T and HepG2 knock-in cbs-R336C cell lines: generated using CRISPR/Cas9 technique.

Results and Conclusions: In yeast, only WY79p.hCBS, but not WY79p.R336C strain, was able to grow in media lacking cysteine. Similarly, HEK293T knock-in cbs-R336C cells failed to proliferate in media deprived from cysteine, demonstrating the blockage of cysteine formation due to the cbs-R336C mutation in both models. Native PAGE-gel analysis demonstrated similar expression levels of the cbsR336C protein, but absence of the active tetrameric conformation present in both wt HEK293 T or WY79p. hCBS cells. We recently started screening of potential drug candidates that might restore R336C-cbs activity in these models. Our previous studies showed that the enzymatic activity of R336C-cbs protein (bacterial purified or crude cell homogenate) can be repaired using cysteamine, a drug used for treatment of cystinosis (Hum Mol Genet. 2015; 24: 7339). Next to cysteamine, therapeutic alternatives, including chaperones and gene therapy approaches, are currently under investigation.
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