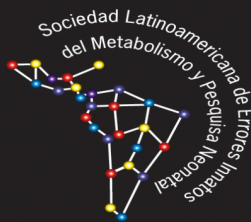


# *Journal of* **INBORN ERRORS of METABOLISM and SCREENING**

**Editor-in-Chief: Roberto Giugliani**



**Latin American Society of  
Inborn Errors of Metabolism  
and Neonatal Screening**



**13<sup>th</sup> International Congress of  
Inborn Errors of Metabolism**  
RIO DE JANEIRO, BRAZIL - SEPTEMBER 5-8, 2017

**SPECIAL SUPPLEMENT WITH THE ABSTRACTS**



## FOREWORD

The *Journal of Inborn Errors of Metabolism and Screening*, the official journal of the *Latin American Society of Inborn Errors of Metabolism and Neonatal Screening*, is pleased to introduce this special supplement with the abstracts accepted for presentation at the *13<sup>th</sup> International Congress of Inborn Errors of Metabolism* (Rio de Janeiro, Brazil, Sep 5-8, 2017).

This supplement includes the 919 abstracts submitted as free communications and accepted for presentation at ICIEM 2017. The abstracts are numbered from 001 to 919, in the order as they appear in the supplement. The abstracts were classified by the authors in one of the 26 categories, listed in Page V. These categories are in sequential order (01 to 26), with all abstracts of the same category in sequence. At the end of the supplement there is an author index, alphabetically ordered by surname, with the number(s) of the abstract(s) presented by each author (not the page number).

This supplement is also available online (open access) at the JIEMS website ([www.iem.sagepub.com](http://www.iem.sagepub.com)),

We hope that this JIEMS supplement contributes to disseminate the scientific output of this major event in the IEM field.



**Roberto Giugliani**  
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# Journal of Inborn Errors of Metabolism and Screening

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Store-operated Ca<sup>2+</sup> entry (SOCE) is a pathway for increasing intracellular Ca<sup>2+</sup> levels regulated by stromal interaction molecule 1 (STIM1), STIM2, and the Ca<sup>2+</sup> channel ORAI1. SOCE-deficient patients suffer from Calcium Release-Activated Calcium (CRAC) channelopathy characterized by immunodeficiency, autoimmunity, myopathy, and anhidrotic ectodermal dysplasia. Several mitochondrial enzymes/complexes depend on Ca<sup>2+</sup> but the source of Ca<sup>2+</sup> required for their function are not entirely clear. We recently showed a cell-intrinsic role of SOCE in human mitochondria (Maus M et al. *Cell Metab.* 2017;25(3):698-712). MitoView Green showed reduced mitochondrial volume in fibroblasts of patients with ORAI1/STIM1 loss-of-function mutations. mtDNA copy numbers and mRNAs expression of selected mitochondrial transcription factors were normal. SDS-PAGE/Western blot analysis showed reduced expression of NADH ubiquinone oxidoreductase subunit-B8, Cytochrome b-c1 complex subunit-2, Cytochrome c oxidase subunit-I, Cytochrome C, Mitochondrial porin and permeability transition pore, etc. Blue native PAGE of isolated mitochondria confirmed reduced expression of CI, CIV and supercomplex CICIII2. SOCE-deficient fibroblasts had reduced mRNA and protein expression of uncoupling protein 2, higher basal mitochondrial membrane potential (MMP) and higher numbers of damaged mitochondria as suggested by increased co-localization of mitochondria and lysosomes and increased MitoKeima reporter activity indicative of lysosomal mitophagy. Oligomycin-induced ATP-synthase inhibition revealed decreased electron transport and proton pumping rates measured as MMP hyperpolarization rates and reduced superoxide production assessed by MitoSOX. Maximal O<sub>2</sub> consumption rates in SOCE-deficient cells were decreased. Skeletal myocytes had reduced CI and CIV function in 2 out of 3 ORAI1-deficient patients. Gene expression of very long chain acyl-CoA dehydrogenase and long-chain fatty acid transporter carnitine palmitoyltransferase 1B was reduced in patient fibroblasts cultured in either high glucose medium or oleic acid (OA) medium followed by starvation in 2 mM glucose medium. Furthermore, SOCE-deficient fibroblasts were lacking a starvation-induced increase in etomoxir-sensitive mitochondrial respiration in OA medium and showed reduced rates of OA beta-oxidation when cultured in <sup>14</sup>C-OA-medium with or without subsequent starvation. Our findings indicate an important new role of SOCE in mitochondrial function.

## 535 - Next Generation Sequencing Improves Mitochondrial Diseases Diagnosis

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**Introduction:** Mitochondrial diseases are a group of rare inherited disorders characterized by extreme phenotypic heterogeneity that can be transmitted by any mode of inheritance, with hitherto no effective therapy options. The recent evaluations of Next Generation Sequencing for mitochondrial disorders have shown that this methodology is more likely to provide a diagnosis, being quicker and cheaper. Since 1993, our group, pioneer in the study of these disorders in our country, has been studying more than 2500 patients with suspicious diagnosis of mitochondrial disorders. The biochemical and molecular approach used, allowed the characterization of many of these patients; however, some of them still remain without molecular diagnosis. **Objectives:** The overall aim of our research project\* was to develop a Next Generation Sequencing strategy to identify nuclear disease causing-mutations in patients suspicious of mitochondrial disorders but without molecular etiology. **Methods:** Next Generation Sequencing was performed in a MiSeq Illumina instrument\*\* using i) a custom mitochondrial gene panel with around 200 genes involved in mitochondria metabolism. Libraries were prepared using SureSelect QXT target enrichment system from Agilent; and ii) the entire human mitochondrial genome enriched by a single amplicon long-range PCR followed by nextera XT workflow. **Results:** Until now we analyzed 56 patients, identifying disease related mutations in 22 of them. These mutations were confirmed by Sanger Sequencing in the index cases and in their relatives. Our project is ongoing and the patients undiagnosed after this first approach will be further selected for Whole Exome Sequencing. **Discussion and Conclusion:** This study is contributing to i) identify the pathogenic mutations in the studied patients (22/56—39%), ii) expand the mutational spectrum in the etiology of these disorders, and iii) propose an accurate genetic counseling. Custom design panels have been widely used for molecular heterogeneous disorders however, the development of this panel will be innovative in our country strengthening our center as a national reference for the study and research of

mitochondrial disorders. \*This Research Project is support by FCT (Fundação da Ciência e Tecnologia) (PTDC/DTP-PIC/2220/2014). \*\*This Research Project is support by NORTE2020 (NORTE-01-0246-FEDER-000014 DESVEN-DAR “DEScobrir, VENcer as Doenças rARas”)

### 536 - Novel Hemizygous Mutation of *TAZ* Gene in a Boy With Atypical Barth Syndrome

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**Background:** Barth syndrome (BTHS; MIM 302060) is widely considered a rare disorder, characterized by cardiomyopathy, neutropenia, skeletal myopathy, and growth delay. The *TAZ* gene encodes tafazzin, a component of the mitochondrial membrane that has been shown to play an essential role in heart development and cardiac function. However, genotype-phenotype correlation has not been clearly defined yet. Although, clinical symptoms are usually present early in infancy, the age of presentation and features of BTHS varies significantly among patients. **Methods and results:** We describe the case of a 6-year-old male with a dilated cardiomyopathy and increased left ventricular trabeculation, dysmorphic features, speech impairment, normal growth, and the absence of elevation of 3-MGA. The boy manifested neither neutropenia nor recurrent infections. The genetic test of genomic DNA from the venous peripheral blood sample was performed by NGS Illumina Tru Sight One Sequencing Panel. No mutations in genes known to cause dilated cardiomyopathy were identified. Hemizygous missense mutation NM\_000116.3: c.608G>T (p.Cys203Phe) in exon 8 of the *TAZ* gene for proband was identified. Multiple sequence alignment of tafazzin revealed that mutation is in a conserved region and is located at a functionally relevant site (in a phosphate acyl-transferase domain). The *in silico* analysis of the identified variant shows it to be as disease causing variant (PolyPhen—probably damaging (0.998), Mutation Taster—disease causing, Provean—Deleterious (4.426)). Detected mutation has been proved by Sanger sequencing using specific primers for exon 8 of *TAZ* gene. His mother was proved to be the carrier of this mutation. **Conclusions:** We describe a patient with dysmorphic features, dilated cardiomyopathy, and speech impairment with novel hemizygous missense mutation in the *TAZ* gene. The investigation for BTHS must be considered in male babies and young boys with dilated cardiomyopathy even if other characteristic features are absent.

### 537 - Diagnosis of Mitochondrial Disorders: The Perspective of a Biochemical-Genetics Testing Laboratory

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The irruption of high-throughput sequencing techniques in the genetic analysis of human Mendelian diseases has dramatically improved the rate of diagnostic success of diseases with complex and expanding spectrums of clinical phenotypes and genotypes such as the primary mitochondrial disorders. The 55 patients (males and females) included in this study are a representative sample of the broad spectrum of symptoms of the patients' population referred to our center from different Hospitals with clinical suspicion of congenital lactic acidosis (CLA), mitochondrial disorder (MD), or even of a less specific -inherited metabolic disorder-. Most of them showed a metabolite profile suggestive of CLA or MD with elevated lactate and/or alanine in blood, and urine and all were analyzed according to our *in house* genetic screen cascade. The framework included a first analysis of nuclear genes by using a Mendelioma massive parallel sequencing (MPS), and a subsequent entire mitochondrial genome (mtWGS) by MPS. Rare variants were filtered and prioritized, and for those patients with only one mutation identified in strong nuclear candidate genes, a functional genomic study based in a case-by case analysis of aberrant transcript present in patients' cells and absent in control samples was applied. For mtDNA variants, we targeted those changes reported in MITOMAP. With this approach, we identified the genetic cause in 24 out of the 55 patients analyzed. Of these, 21 patients harbored 30 disease-causing changes, 12 of them new, in 16 known nuclear genes. Other three patients carried known point mutations in mtDNA: G8719A (*MT-ATP6*), T10158C (*MT-ND3*) and G13513A (*MT-ND5*). *In silico* predictions supported the pathogenic role in each case. Segregation analysis in parents' DNA confirmed their carrier condition. Finally, cDNA analysis of other three patients with only one change detected in *GFMI*, *ARALAR* or *MRPL3* concluded with the identification of the deep intronic c.689+908G>A in *GFMI* gene and left undiagnosed the other two. Up to now, our pipeline has allowed to diagnose a 44% of the patients analyzed. Beyond the use of genetic diagnosis strategies based in whole exome or RNA sequencing, the identification of specific metabolic signatures lying downstream of the primary mitochondrial lesions and the unification of criteria to classify clinical symptoms, will contribute to improve the MD diagnosis and treatment. PI12/02078; PI16/00573; MINECO-FEDER. Fundación Isabel Gemio