Patient-Researcher Collaborations Promote the Development of Personalized Medicine for Lafora Disease – A Childhood Dementia and Epilepsy

Kit Donohue[1,2], Lena Ismail[1], Kia Markussen[2], Maya Abul-Khoudoud[2], Pascual Sanz[3], Jose Serratosa[4], Maria Macchio[1,4], Berge Minassian[5], Ramon Sun[6], Craig Vander Kooi[6], and Matthew S Gentry[6]

[1] Chelsea's Hope Lafora Children Research Fund, [2]University of Kentucky College of Medicine, [3]Instituto de Biomedicina de Valencia, [4]Hospital Universitario Fundación Jiménez Díaz,, [5]University of Texas Southwestern Medical Center, [6]University of Florida College of Medicine

Lafora Disease: An Introduction

Lafora disease (LD) is a fatal childhood dementia and epilepsy. Patients develop seemingly normal as children, and are typically diagnosed during adolescence, when the disease presents as a form of progressive myoclonus epilepsy, leading to neurodegeneration, movement disorders, and childhood dementia. It is known that patients with Lafora Disease have mutations in either *Epilepsy, Progressive Mycolonus 2A* (*EPM2A*), or *Epilepsy, Progressive Mycolonus 2B* (*EPM2B or NHLRC1*), which code for the proteins laforin and malin, respectively. Loss of function in laforin or malin leads to the aggregation of aberrant glycogen in tissues throughout the body. Multiple therapies are in development for LD patients, however, recent studies suggest that early detection will be critical for effective treatment of LD patients.

Laforin is the only known mammalian phosphatase that can remove phosphate from glycogen, and malin is an E3 ligase that has been shown to ubiquitinate enzymes involved in glycogen synthesis and degradation. Together, these proteins play critical roles in regulating glycogen metabolism. Disease causing mutations occur throughout each protein, suggesting multiple roles for both laforin and malin in glycogen regulation. Given the diversity of disease-causing mutations in these proteins, the loss of function varies and results in varying progression through the disease. Therefore, appropriate selection of cohorts for clinical trials and future treatment of LD patients will require a personalized medicine approach and the establishment of genotype-phenotype correlations.

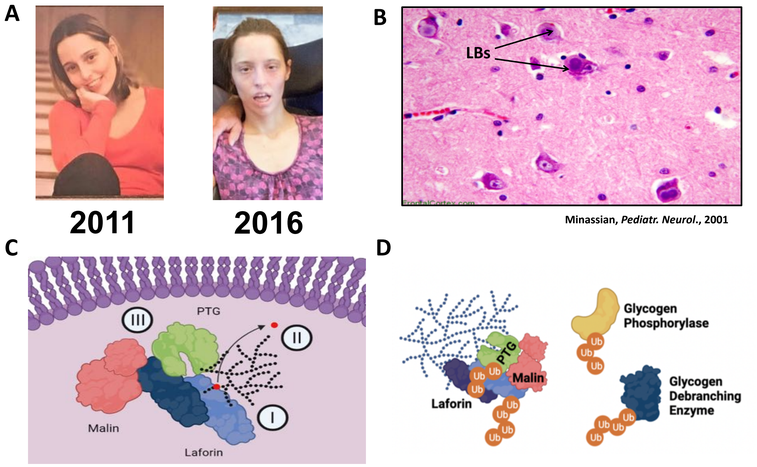


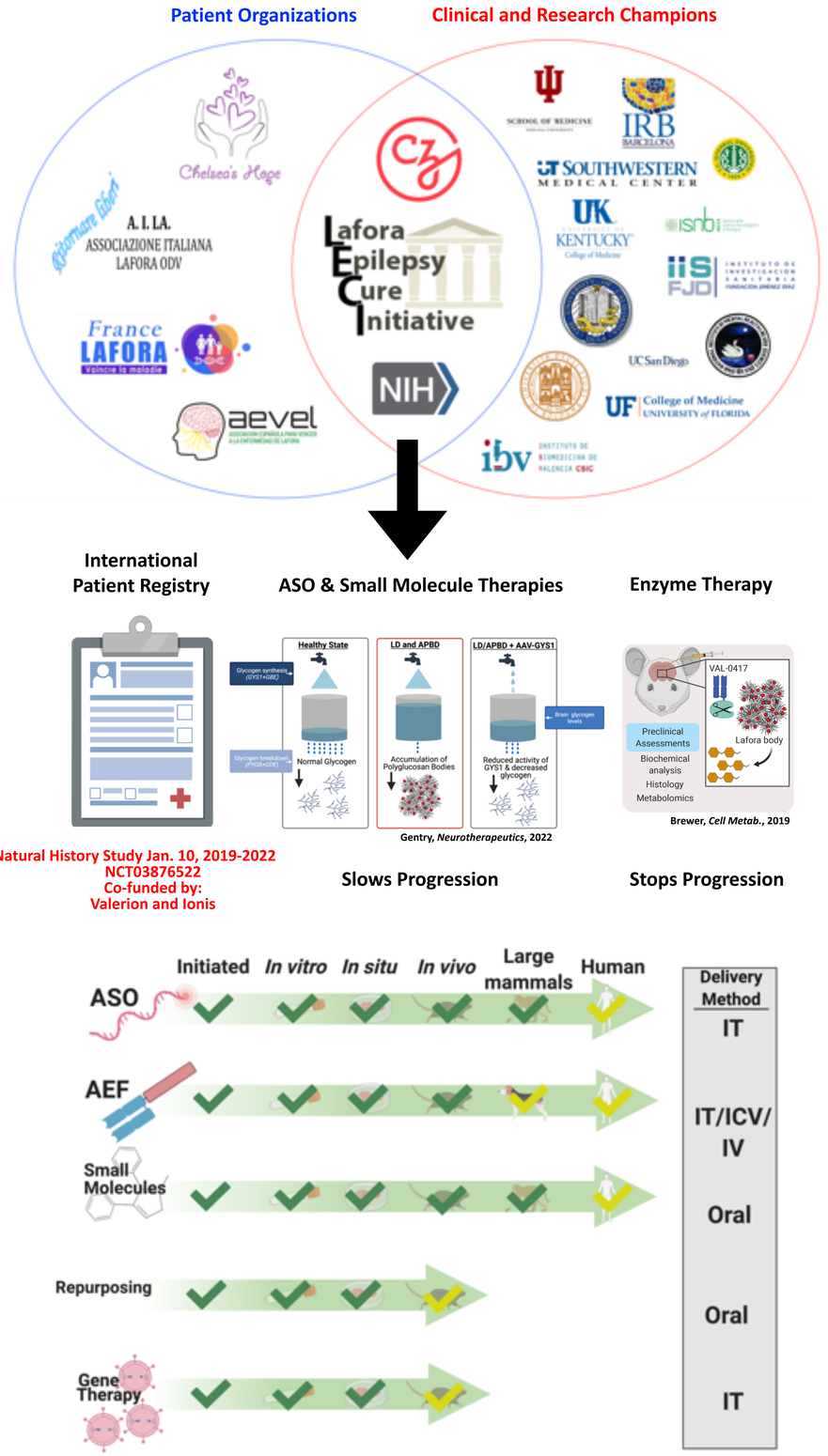
Figure 1. Overview of Lafora Disease, Laforin and Malin. A) Photo of an LD patient 6 years and 11 years after diagnosis. The patient passed in 2016. **B)** PAS-stained brain tissue, where the dark fuchsia stains highlighted with arrows are aggregates of aberrant glycogen, termed Lafora Bodies (LBs). **C)** Diagram of the critical functions of laforin for glycogen metabolism: i) glycogen binding ii) the dephosphorylation of glycogen and iii) scaffolding for malin and PTG. **D)** Diagram of the known functions of malin, an E3 ligase that ubiquitinates laforin, PTG, glycogen phosphorylase and glycogen debranching enzyme.

Chelsea's Hope: Our Mission

Our mission is to improve the lives of those affected by Lafora Disease and help accelerate the development of treatments.

To achieve this mission, Chelsea's Hope brings together multiple LD and rare disease patient organizations, expands the research network through annual symposia and quarterly research roundtables, and provides educational resources and support for LD families

Collaborations Toward Therapeutic Development



LD Hallmarks & Potential Biomarkers

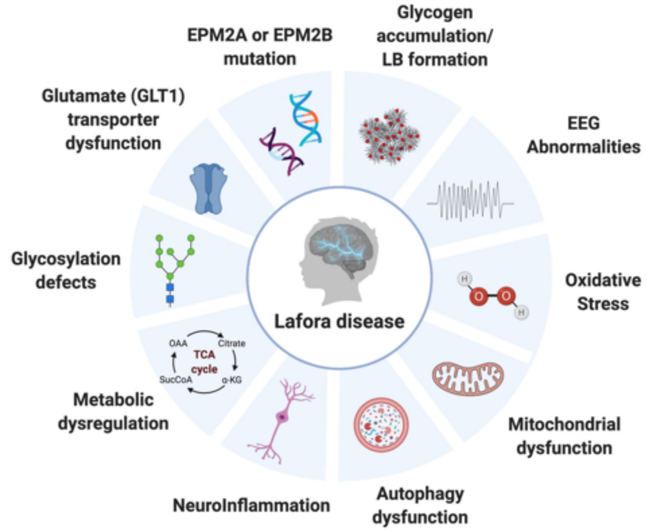


Figure 2. Research collaborations clarify multiple hallmarks of LD. The 2020 Annual Symposium brought together speakers who highlighted known and novel biomarkers within LD patients, including glycosylation defects and metabolic dysregulation (Markussen, Epilepsy Behav., 2021)

Defining Patient Cohorts

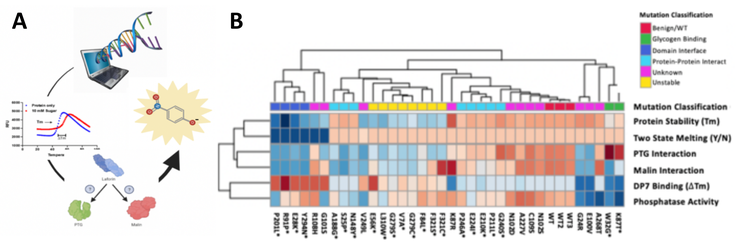


Figure 3. Defining genotype-phenotype correlations for laforin. A) Graphic pipeline for characterizing function loss in laforin using bioinformatics, stability and carbohydrate binding assays, protein-protein interactions, and dephosphorylation. **B)** Using an adaptation of MetaboAnalyst, biochemical assays were recorded in standardized units and clustered in a heatmap (Euclidian, average clustering) aligning novel mutation profiles with previously characterized patient mutations (Brewer, iScience 2021). This lays the groundwork for defining patient cohorts for personalized diagnosis and treatment (Donohue, 2023).

Future Projects

- **Create a publicly–accessible platform to provide new researchers with the tools to study Lafora Disease mechanisms and therapies**
- **Bring together clinicians to identify novel biomarkers for clinical trials**
- **Utilize the Research Roundtable and Annual Symposium to expand our network to include other Glycogen Storage Diseases that could benefit from therapies that reduce glycogen aggregation**

Acknowledgments

This research and organizational development was supported by National Institute of Neurological Disorders and Stroke (R35 NS116824, P01 NS097197-01), and the Chan Zuckerberg Initiative Rare as One and Neurodegeneration Challenge Network Grants. Images created with Biorender.com