ahcf | alternating hemiplegia of childhood foundation

July 2024
Research Newsletter

Thank you to all who help support, volunteer, and research for our AHC Heroes!

AHCF Volunteers Fund Record Breaking Research

Congratulations to every AHCF volunteer for helping to fund a record amount of AHC research. Over the last ten years, YOU made it possible to fund over **$2.5 million** in AHC research! What an amazing accomplishment!

When the ATP1A3 mutation was discovered in 2012, we were thrilled to be the foundation that funded the project which answered the question, **"What causes AHC?"** Building on this success, we stepped up our research efforts and granted over $2.5 million in research worldwide. Some of the programs we funded included: Broad Institute, Brown, Duke, Harvard, Leeds, Northwestern, UT Southwestern, Utah, and Vanderbilt.

Volunteers worked so hard fundraising for the last ten years that **an additional $687,000 in funding went to support research conferences, family meetings, symposiums, webinars, and neurology conferences.** This research effort helped educate clinicians, researchers, and scientists about AHC while building an amazing community. Together, AHCF volunteers invested over $3.2 million in AHC research efforts. Such amazing work by an outstanding group of volunteers! We are so proud to be part of this community with you.

We hope you enjoy reading a little about the research you made possible over the last year.

Therapeutic Oxygen Research Funded

The AHCF is excited to join an international group of AHC family foundations in funding a multicenter, randomized, placebo-controlled, double-blind crossover study in France. The principal investigators are Dr. Eleni Panagiotakaki and Dr. Emmanuel Roze. The official title of the study is **Oxygen Therapy as an Acute Treatment for Dystonic and/or Plegic Attacks in Alternating Hemiplegia of Childhood.** The aim of the study is to assess the effect of high-flow oxygen administration (against placebo) as an acute treatment of dystonic and plegic attacks.

The primary outcome will be the proportion of motor attacks stopped 30 minutes after the beginning of motor symptoms over 5 weeks. Some of the secondary outcomes will be:

- the median duration of dystonic and plegic attacks
- the evaluation of the quality of life for patients and caregivers

- the frequency of motor attacks
- the consumption of sedative treatments (number of doses used)
- the proportion of dystonic and plegic attacks respectively stopped 30 minutes after the beginning of motor symptoms
- the number and proportion of treated attacks

The international collaboration on this project is exciting and we look forward to sharing the results of the study as soon as they are available.

ASO & C. elegans

AHCF Building on Success Funding Dr. Hart's Research at Brown University

In 2023, Dr. Anne Hart began developing a C. elegans model of AHC in a collaborative research project funded by AHCF, Cure AHC and Hope for Annabel. C. elegans are a worm animal model that provides different opportunities to expand AHC research. We are now fortunate to fund phase two of this project which will finish characterizing D801N, E815k, and L839P lines. This work will hopefully increase our understanding of molecular pathways leading to AHC. We look forward to hearing more from Dr. Hart later this year.

Read More about Dr. Hart

Expediting ASO Research

This spring, we were thrilled to have an opportunity to expedite the pilot mouse ASO study which was originally funded in the Fall of 2023. By combining our funding efforts with For Henry AHC and Cure AHC, we were able to give the project an extra boost with this additional funding. Stay tuned for details on how the project wrapped up later this year.

Here is a link to an article discussing the possibilities and limitations of ASO therapies

Link to Article

TOP AHC Experts Join AHCF

Welcome Dr. Kathryn Swoboda to the AHCF Medical Advisory Board (MAB)

Welcome Dr. Matthew Campbell to the AHCF MAB
The AHC Foundation Board of Directors is honored to announce that Dr. Matthew Campbell is

Welcome Dr. Andrew Landstrom to the AHCF MAB

Andrew Landstrom, MD, PhD is an Associate Professor of Pediatrics

The AHC Foundation Board of Directors is honored to announce that Dr. Kathryn Swoboda is the new Senior Advisory Consultant to the foundation. Dr. Swoboda will once again be sharing her decades of AHC experience with the foundation but in a new and exciting way. Both the foundation and medical advisory boards will now benefit from the clinical and research experience of Dr. Swoboda while carrying out the foundation's mission. Together, we look forward to implementing a research strategic plan that prepares the community for clinical trials, provides opportunities to educate and recruit new AHC clinicians, develop AHC management guidelines for families and practitioners, and bring new treatments to the AHC community. All of this in hope of achieving our One Mission of Ending AHC.

Please join us in welcoming Dr. Swoboda to this new and exciting opportunity with the AHC community.

joining the AHCF Medical Advisory Board. Dr. Campbell is Professor in Genetics and Head of Department at the Smurfit Institute of Genetics in Trinity College Dublin, Ireland. He is originally from Dublin and graduated with a degree in Biochemistry from University College Dublin (UCD) in 2002 and went on to complete a PhD in 2006 at the same institution. In the same year, he moved to Trinity College Dublin and conducted postdoctoral research in medical molecular genetics. In 2013, he was awarded Science Foundation Ireland's (SFI) President of Ireland Young Researcher Award (PIYRA) which allowed him to establish his own research group in TCD. Since then, he has received numerous additional awards for his research which focuses on understanding the role of the so-called blood-brain barrier (BBB) and blood retina barrier (BRB) in healthy and diseased states. In 2022, his group identified a mutation in the key BBB gene CLDN5 that causes alternating hemiplegia of childhood (AHC) and microcephaly. He is the founder and Director of the Neurovascular Genetics Unit at TCD and has over 20 years of research expertise in the area of blood brain and blood retina barrier biology. He sits on the scientific advisory board of the Moorfields Hospital Charity as well as the UK charity Sight Research UK.

Please join us in welcoming Dr. Campbell to this new and exciting opportunity with the AHC community.

(Division of Cardiology) and Cell Biology at Duke University School of Medicine. He is a pediatric cardiologist with expertise in heritable arrhythmias, cardiomyopathies, and genetic cardiac diseases. He leads an NIH-funded lab which studies how heritable arrhythmias, cardiomyopathies, and congenital heart disease develop with a goal of developing new therapies to treat these life-threatening diseases. He has led preclinical work that has found new therapies for heritable cardiac conditions, including gene therapy targets. He also leads clinical research in predictive cardiovascular genomics with a goal of identifying who is at-risk of developing heritable cardiac disease, before disease develops.

Please join us in welcoming Dr. Landstrom to this new and exciting opportunity with the AHC community.

AHCF Helps Fund 2024 ATP1A3 Symposium in Spain

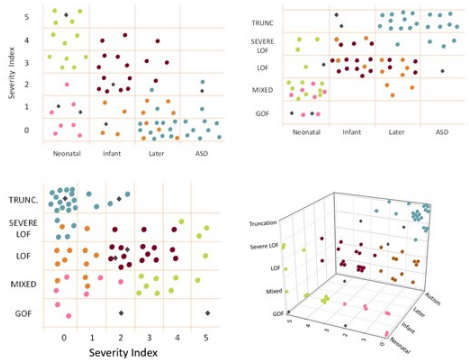
The Board of Directors are pleased to announce our financial support of the 2024 ATP1A3 Symposium in Barcelona, Spain. The directors recently voted to provide $5,000 in financial support to the symposium. The foundation will also provide an additional $5,000 in stipends to send U.S. representatives to the symposium. This

$10,000 investment in furthering the study of the ATP1A3 gene mutation is made possible through the generous donations of our AHC community.

Find Additional Information

New Research from Dr. George

Just over ten years ago, the foundation was thrilled to welcome Dr. Al George to the AHC community when we began funding his research with Dr. Kevin Ess at Vanderbilt University. In addition to continuing to move AHC research forward, Dr. George is an active leader within the AHC community. We'd like to take a moment to congratulate Dr. George on the publication of an important article in the April 2024 journal, Brain. This paper advances knowledge of the relationship between variant function and clinical disease expression that will be valuable for identifying appropriate patients for clinical trials and in selecting efficient clinical outcomes. Congrats Dr. George.



Expanded clinical phenotype spectrum correlates with variant function in SCN2A-related disorders

Variants in the SCN2A gene cause epilepsy, autism and other severe neurological impairments. Berg et al. show that the impact of an SCN2A variant on Nav1.2

Read More

Spring Update on AHC Prime Editing Research

In case you missed the **social media posts**, we want to update you on some exciting news related to our gene editing project. Over the last several months, the Liu Lab has tested their gene editing strategy in AHC mice at the Jackson Laboratory. Preliminary results are encouraging.

The Liu team has found that treatment with prime editors can correct the Atp1a3 D801N mutation in the mouse brain and improve multiple clinically-relevant symptoms in D801N mice.
This is the first reported in vivo rescue of a neurological

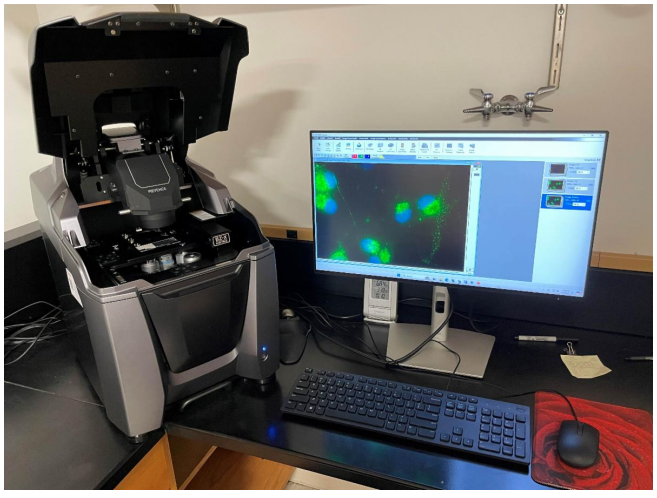
disease with prime editing.

This data is the first piece of evidence that prime editing may work as a therapeutic strategy in vivo in AHC. We are still many steps away from a therapy for AHC patients, but this result is a very positive first step on the long road ahead.

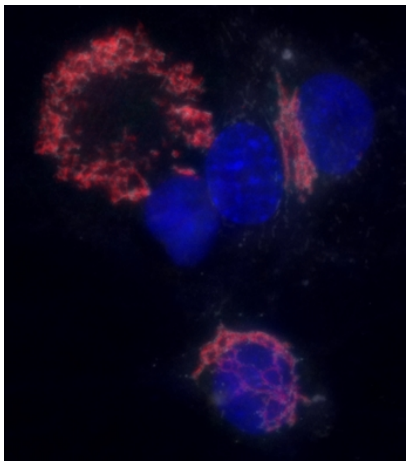
These findings are also the result of many years of effort from Drs. David Liu, Alex Sousa, and the Liu lab, and from Drs. Cat Lutz and Markus Terrey, and their colleagues at Jackson Laboratory. We are truly grateful to partner with such an incredible team.

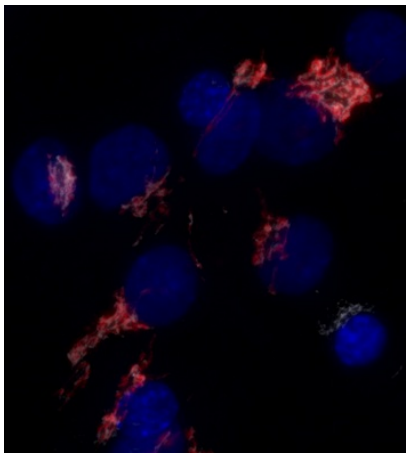
Following Up on Funding with Dr. Kathleen Sweadner

About a year ago, the AHCF helped fund a state-of-the-art microscope to advance AHC research. Here is an update on how this important equipment is working to End AHC. Dr. Kathleen Sweadner at Massachusetts General Hospital has been studying why some ATP1A3 variants produce AHC, and some produce different syndromes, either milder or more severe. Her belief is that if we understand the mechanisms, we will be in a better position to find therapies. Besides losing activity, some mutations in ATP1A3 impact its synthesis in cells. This is the fluorescence microscope the foundations purchased for her to use. It is an instrument with sophisticated software.



Below are images of the Golgi apparatus in wild type and G947R cells. Blue stains the nucleus, and red and white are two different Golgi markers. The G947R cells have a larger number of enlarged Golgi than the normal cells. These are pictures of patient-derived iPSC neurons that were grown in Dr. Al George's lab.





Be A Part!

With your help, we can continue researching and building our network. We now have the ability to accept monthly recurring donations, or you could have a fundraiser in your area! Simply click here to find out how YOU can help!

Find Out Now

If you would like to join the AHCF Research Committee, please reach out to **Vicky@ahckids.org**

Newsletter Editor: Sylvia Pollard

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