



# One Mission: End AHC!



YOUR ALTERNATING HEMIPLEGIA OF CHILDHOOD FOUNDATION NEWSLETTER

November 2017

2000 Town Center ■ Suite 1900 ■ Southfield, Michigan 48075



## A MESSAGE OF THANKS

### Happy Thanksgiving to the AHC Community

On Thursday, November 23, we celebrated Thanksgiving. This national holiday in the United States is a time for us to celebrate with family and friends. It's also time for us to reflect on our many blessings. And, it's a time for us to give thanks.

So, in that spirit, I want to thank you. **Thank you for supporting the foundation and AHC community.** I want to **thank you for sharing the mission of the foundation and helping to raise money for AHC research.** And finally, I want to **thank you for loving and caring for a person with AHC.** Wherever you live, in the spirit of the holiday, I wish you a very Happy Holiday Season!

Lynn Egan  
President and Family Support

## SUPPORT AHCF THIS HOLIDAY SEASON

### Cyber Monday & Giving Tuesday are the 27<sup>th</sup> & 28<sup>th</sup>



## AMAZONSMILE

Supporting: Alternating  
Hemiplegia Of Childhood

Whether you're getting a jump start on holiday shopping or making a routine online purchase for yourself, **remember to use AmazonSmile and your purchases** will help to support the AHC Foundation!

Another way to show support for AHC Research is by participating in #GivingTuesday and making a gift of any amount to the AHC Foundation.

## AHC Community in ACTION

### The AHCF Year End Campaign is Ready for You in 2017!

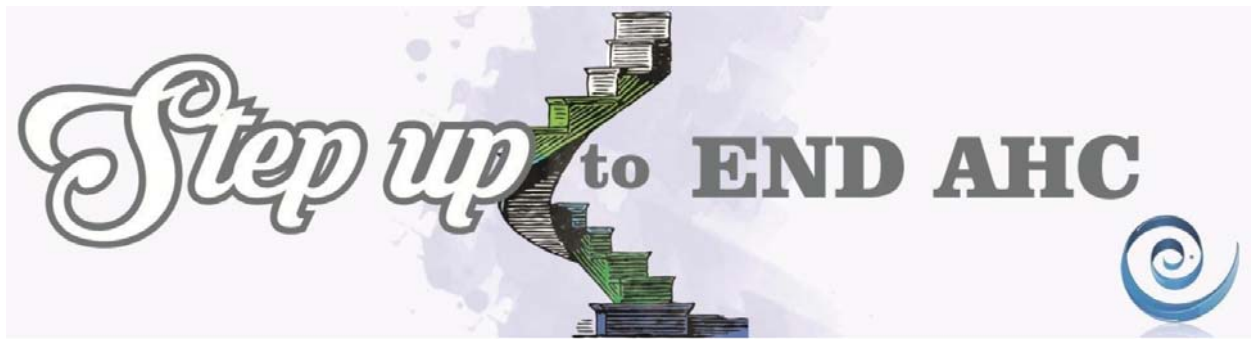
The AHCF Board of Directors is pleased to be building on the huge success of our campaign last year and continue once again with the **Step Up to End AHC 2017 Campaign.**

**Our campaign is a fun and simple** way for everyone in the AHC community to come together and help raise money for the AHC research taking place at Northwestern and Vanderbilt Universities next year.

We'll provide you with all of the tools you need to **share this important message** with your friends and family during November and December. While everyone is very busy during this time of year, we'll make increasing awareness about AHC a spirited and joyful experience.

When you support the **Step Up to End AHC campaign**, you are helping the AHCF achieve its mission to **fund research, promote year-round education, and provide families with much needed support.** All of your efforts will directly affect the future of every person living with AHC!

**YOU CAN TAKE THE NEXT STEP TOWARDS OUR ONE MISSION: END AHC!**



### End of the Year Campaign

The struggle to fund research never ends! We need as many families as possible to join us. We are asking every family to create a page in our yearly campaign and **make \$500 your goal - not to donate the money but to raise it through a fundraiser or email/letter campaign.**

Remember this is for all the AHC kids, young and old. **Most people donate to their favorite causes at the end of the year - encourage them to make AHCF that cause! The process is super easy.**

#### HELPING TO END AHC TAKES ONLY FOUR EASY STEPS:

##### CLICK ON THIS LINK:

<https://www.firstgiving.com/AHCF/step-up-to-end-ahc-2017>

**CLICK ON** the green Fundraise button

**FILL OUT** the page and upload a picture

**SHARE** your page with friends and family with a simple ask for donations



**This year's campaign is to support two projects.** The first project is the second half of the 6th phase, "Molecular Physiology and Pharmacology of ATP1A3 Mutations in AHC". The project builds upon their previous work studying **the functional impact of the three most common mutations in the ATP1A3 gene.** This will include testing the ability of several compounds identified through computer modeling to restore pump function. They will also use human stem cells that were differentiated into neurons to study electrophysiological dysfunction as well as the possible reversal of these abnormalities by treatment with candidate compounds.

#### FUNDRAISING IS FUN!

**SET a GOAL** and try to achieve it. Start with \$500 as a goal.

**SOCIAL MEDIA** makes sharing your story easy and quick.

**GET FAMILY INVOLVED** and focus on giving vs. getting.

**NEW EXPERIENCES** with fundraising are rewarding.

**CELEBRATE** your success during the holidays



The second project will support the Antibody Acceleration Project. Dr. Kevin Ess and his team at Vanderbilt University are **at the half way point of generating and validating highly specific antibodies** targeting against the alpha 3 and alpha 2 subunits of the Na/KATPase. These antibodies will not only support the work that Dr. Ess and Dr. George are doing but will be shared with the any researcher who is working on AHC/RDP and CAPOS, all with the ATP1A3 mutation.

The AHC Foundation has garnered enormous support financially, as well as through the time and talents of volunteers, applied toward our mission to support families, educate the community, and advance research. The AHCF understands that good stewardship of the funds donated to us is of the highest priority for those who **contribute to our mission to END AHC!**



## AHC INFO EXCHANGE

### Report from Japan ATP1A3 Symposium

A group of scientists, researchers and doctors gathered in Japan on September 21-22, 2017. Dr. Alfred George attended the symposium and provided the AHCF with a summary of the sessions. We are grateful for Dr. George's thorough and thoughtful report of this important conference.

The **6th Symposium on ATP1A3 in Disease** was held in Tachikawa City, Tokyo, Japan September 21-22, 2017. The conference was the most well attended of all ATP1A3 conferences so far with 190 attendees including several physicians, trainees and researchers from Japan who are new to the field. **The host, Dr. Masayuki Sasaki**, received a standing ovation at the conclusion of the meeting for his outstanding hospitality and organization. Highlights of the meeting are summarized in this report. Because many researchers presented unpublished results, only the general nature of some presentations can be reported.

The opening talk **on Day 1** was given by **Dr. Sasaki** who presented the history of major milestones in the field including the original clinical description of AHC, discovery of the gene and the expanding spectrum of neurological disorders associated with ATP1A3.

Following this overview, **Dr. Rosewich** discussed specific challenges and dilemmas associated with diagnosing AHC and related disorders. He emphasized the diagnostic framework presented in the 2017 Neurology Genetics paper from the AHCF-sponsored workshop, which called for standardized definitions of neurological features of ATP1A3-related disorders.

Next, **Dr. Brashear**, provided an update on clinical studies on RDP including preliminary findings from an ongoing NIH-funded study of brain imaging. These studies are seeking to identify and validate diagnostic features of RDP that can be acquired by MRI and other imaging tools available in the clinic.

Additional presentations by **Drs. Sakai and Ishihara** described cases with atypical clinical presentations including that of an infant with catastrophic epilepsy in which ATP1A3 mutations have been discovered.

Two presenters discussed progress in analyzing data from large patient registries. **Dr. Panaiotakaki** reported on the International AHC Consortium, which has so far enrolled 155 subjects. She discussed findings on clinical features of patients with the most common mutations, some natural history and clinical outcome data, and further evidence supporting the association of the E815K mutation with generally more severe features.

**Dr. Swoboda** updated the conference on her efforts to curate the AHCF registry comprised of approximately 300 subjects and more than 1000 biospecimens gathered mostly from North and South America. She further described her current collaborations with investigators at the Broad Institute at MIT to examine gene expression in blood samples, which they hope will uncover novel biomarkers of the disease.



Throughout the conference, there were discussions of the importance of finding biomarkers to augment efforts to evaluate treatment success and follow the progress of the disease. **Dr. Balestrini** reported a follow-up of their study showing evidence of abnormal heart activity (e.g., abnormal electrocardiographs) in AHC. They now have 116 patients enrolled in the study (96 AHC cases).



Dr. Alfred George

## AHC INFO EXCHANGE

### Report from Japan Continued

**Dr. Sweadner** presented an advanced analysis of the location of mutations within the ATP1A3 protein structure and contrasted this with ATP1A2 mutations. There were general correlations between the location of mutations within the protein and the clinical severity of the disease. She shared an in-depth analysis of mutations that were localized to a specific protein region called the P-domain, which has essential functions.

Later in the conference, Dr. Sweadner offered caution about the naming of ATP1A3 mutations and emphasized the importance of using a specific reference sequence of the gene to allow so that mutations are designated consistently. Unfortunately, as she pointed out, some genetic testing laboratories and population genetic resources (e.g., the Exome Aggregation Consortium or ExAC) use a different reference sequence.

**Dr. Apiera** gave a brief, but exciting unscheduled presentation to report their recent discovery of a mutation in ATP1A1 associated with a severe, life-threatening movement disorder drug-resistant epilepsy. This is the first human disorder associated with mutations in this gene.



**Dr. van den Maagdenberg** gave an update on efforts to find additional AHC genes to help explain why 15-20% of AHC cases do not have obvious ATP1A3 mutations.

Their efforts have revealed that some ATP1A3-negative cases, in fact, do have mutations in this gene revealed upon further analysis. He reviewed evidence supporting involvement of at least two other genes but cautioned about the need to verify the diagnosis in these cases.

**Dr. Ishii** reported on the apparent effects of oral ATP therapy in flunarizine-refractory AHC, which was published previously. The specific case was that of a Chinese boy with onset of hemiplegic attacks after age 2 years who was treated with escalating doses of an over-the-counter preparation of ATP. The clinical response to the therapy was notable for reduced attack frequency, improved motor function and improved performance in school. There was no pharmacological data provided on the treatment leaving many in the audience uncertain about the rationale and mechanism for using ATP in AHC.

**Drs. Rosewich and Mikati** commented that attempts to treat patients in their clinics with ATP had not been effective although admittedly the doses tried were lower than that used in the Chinese boy. There were many unanswered questions leaving most attendees with the sense that more fundamental knowledge is needed before recommending this therapy.

The conference transitioned from clinical and genetic themes toward a more basic science emphasis including 3 lectures highlighting ground breaking research on neurological diseases being performed in Japan given by **Drs. Okano, Hoshi and Matsuda**. A very special lecture on the structure of ion transporting ATPases was given by **Dr. Toyoshima**.



**Your Dollars Matter Most.** Our foundation is 100% donor-supported. Help improve the quality of life of children with AHC today...with your donation.

## AHC INFO EXCHANGE

### Report from Japan Continued



The second day of the conference included talks on mouse models, cellular models, structural and functional investigations.

Three groups reported on their progress in modeling AHC in mice with a focus on testing various strategies to alleviate major neurological features. **Dr. Clapcoate** summarized his group's efforts to exploit three independent strategies including a genetic strategy, an ATP1A3 modulator (rosafuroxin) and a proprietary diet. **Dr. Lykke-Hartmann** reported on neurophysiological studies of the D801Y mouse model and showed previous data demonstrating the ability of

flunarizine to attenuate cold-water induced hemiplegic and dystonic attacks in the mice. **Dr. Mikati** showed new data on the effectiveness of flunarizine and an undisclosed investigational compound on mice with the E815K mutation. Flunarizine was effective at shortening the duration of hemiplegic attacks but didn't prevent seizures or long term behavioral deficits. He commented that these mice are extremely fragile and have a high mortality rate thus limiting the extent to which pharmacological studies can be performed.

Three groups presented their findings on the functional properties of various ATP1A3 mutations. **Drs. Bente and Petrou** demonstrated unique functional features of the E818K mutation associated with CAPOS syndrome and presented detailed information about the mechanism for the dysfunction of this and other mutations.

**Dr. Koenderink** discussed his findings on ATPase activity of several mutations and offered to study the function of all known ATP1A3 mutations provided that research funding was available. The last presentations of the conference were by **Drs. Ess and George** who reported their findings using patient-derived induced pluripotent stem cells (iPSCs) to create nerve cells for laboratory investigation of AHC. They presented their data showing successful use of this 'disease in a dish' approach to determine fundamental cellular dysfunction of the G947R mutation as well as a novel mutation causing abnormal gene splicing.

A special evening event was hosted by the **Japanese AHC Foundation** and featured presentations by representatives of **CURE-AHC and the French AHC Foundation**. Several Japanese families were present as well as parents from many other countries. **An emphasis was made on the important role of family organizations in raising awareness of the disease in communities, and raising funds to support research.** Much of the research presented at this conference has been made possible by generous donations of these and other foundations.

**The 7th Symposium on ATP1A3 in Disease will be held in October 2018 in Chicago. The AHCF will serve as the host organization.**



Dr. Sasaki & Dr. Swoboda

The AHCF is thankful to all of the doctors, researchers and scientists working to end AHC.

**Keep up the great work.**

Through research, education and family support, we have **ONE MISSION: END AHC!**