

Propionic Acidemia Foundation

VOLUME 1, ISSUE 4

SPRING 2008



Date: Saturday, June 21st

Time: 11:00 am - 5:00 pm

**Place: The Harding Home
2130 Hart Ct., Lexington,
Kentucky 40502**

**R.S.V.P. to Julie Harding at 859-269-9860 or to
paf@pafoundation.com**

**This is a great opportunity to meet and learn from
other PA families. Please contact Julie if you have
any questions! We hope to see you there!**



Lucy Harding, Age 10

Volunteers Needed

PAF is run exclusively by volunteers. There are several projects that PAF is working on that could use your help including family mentoring, fundraisers, writing articles and surfing the internet. If you would like to donate some of your time, please contact us by email at paf@pafoundation.com or on our toll free line. 877-720-2192.

WE NEED YOU!

FOUNDATION NEWS

- Propionic Acidemia Foundation is pleased to announce our new collaboration with the National Urea Cycle Disorders Foundation in Jointly Funding a Post Doctoral Fellowship. More on Page 6.
- PAF was invited to exhibit at the Society for Inherited Metabolic Disorders (SIMD) conference in March in Pacific Grove, California. The ability of PAF to attend conferences like SIMD and network with medical professionals who treat and research PA is critical in meeting our mission of finding better treatments and a cure for PA and generating additional interest in the medical community.
- Dr. Jan Kraus has completed his latest research project and his results have attracted interest from the medical community. PAF recently awarded Dr. Kraus a \$30,000 grant for his new project. More on page 2.
- PAF is excited to welcome two new board members. Janice Boecker and Jennifer Mouat joined the PAF in January 2008.



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UPDATE ON DR. KRAUS' LATEST PA RESEARCH

*Dr. Jan Kraus' Laboratory, UCHSC, Dept. of Pediatrics,
University of Colorado School of Medicine*

Propionic acidemia (PA) is a devastating disease: one third of affected infants die in early infancy. PA is caused by a deficiency of an enzyme called propionyl CoA carboxylase, or PCC for short. Two genes, PCCA and PCCB, determine how this complicated enzyme is made. The enzyme deficiency in PA is caused by changes (mutations) in either PCCA or PCCB.

PA follows a recessive inheritance pattern: a person with PA has either two mutated copies of PCCA or two mutated copies of PCCB. If each parent carries one mutation in the same gene then there is a 1 in 4 chance in each pregnancy that the child will inherit both mutations and be affected with the disease.

We are currently one of the few laboratories in the world that systematically studies the biochemistry and molecular genetics of this disorder. In other words, we determine which patients are affected with the disease and what mutations they carry.

We are also trying to discover how the mutant enzyme subunits are folded into shape before PCC is assembled. To be biologically functional, PCC, which is composed of six alpha and six beta subunits, must assemble and fold correctly inside the cell. Some mutations are known to affect the ability of the subunits to fold, and when this happens little or no functional PCC is made.

We have screened a large number of chemicals called chaperones to see which ones might prevent the problem of mutant enzymes becoming inactive through improper folding. We have so far found that some of the chaperones allow some of the mutant enzymes to become fully active but we have a long way to go. There are over 100 mutations to work through and there are many chaperones to test.

We have been doing our research with a bacterial expression system in which mutant PCCs are able to interact with the chaperones. Later on, we will have to test if the chaperones work in cells obtained from the patients' own skin.

The results of these investigations are now being written up for a major medical journal. Our hope is to be able to develop a treatment using this approach that will clinically benefit a number of PA patients in the future.

“We are currently one of the few laboratories in the world that systematically studies the biochemistry and molecular genetics of this disorder.”

-Dr. Jan Kraus

Another area we are exploring is crystallization of the enzyme and determination of its 3D structure. Why is this important? Solving the structure of the enzyme is essential for at least two reasons: First, the structure would allow us to predict the impact of each human mutation on the function of the enzyme; second, any meaningful design of treatment drugs should be based on the enzyme's structure.

On the clinical front, we are involved in a large international study of at least 40 patients with PA. We aim to improve treatment and clinical outcomes by comparing, or correlating, the results of their particular PCC mutations with the clinical course of their disease. Defining PCC mutations will also improve newborn screening and help affected families to ascertain whether family members are carriers.

\$30,000 GRANT AWARDED

In 2008, Propionic Acidemia Foundation awarded Dr. Kraus a \$30,000 grant to determine the 3D structure of the PCC enzyme titled, “Crystallization and structure determination of human propionyl CoA carboxylase.”

Why is this important? Solving the structure of the enzyme is essential for at least two reasons:

1. The structure would allow us to predict the impact of each human mutation on the function of the enzyme;
2. Any meaningful design of treatment drugs should be based on the enzyme's structure.

We are thankful to Dr. Kraus's dedication in helping find better treatments and a cure for propionic acidemia.

ANAPLEROTIC THERAPY IN PROPIONIC ACIDEMIA

Nicola Longo, Marzia Pasquali, Eduard Gappamier, Carrie Ashurst, Sharon Ernst. Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT 84132.

The objective of this project is to define whether nutritional supplements (ornithine alpha-ketoglutarate, glutamine, or citrate) capable of filling-up the citric acid cycle (anaplerotic therapy) can improve hyperammonemia, glutamine levels, and outcome in patients with propionic acidemia. Ornithine alpha-ketoglutarate, glutamine, and citrate are commonly used as nutritional supplements specially by athletes to increase muscle strength. They can be mixed with formula or other foods.

Propionic acidemia is caused by deficiency of propionyl CoA carboxylase that impairs the supply of succinyl CoA to the citric acid (Krebs) cycle. The Krebs cycle is responsible for obtaining energy from food in the form of ATP. ATP is essential for muscle contraction and correct functioning of all organs including the heart, the kidney, and the pancreas.

Patients with propionic acidemia develop hyperammonemia at birth that recurs during episodes of metabolic decompensation. We found that plasma levels of the amino acids glutamine/glutamate are reduced in patients with propionic acidemia and decrease, rather than increase (like in urea cycle defects or other types of hyperammonemia) with hyperammonemia. Since alpha-ketoglutarate is the main source of endogenous glutamate/glutamine synthesis, our hypothesis is that chronic hyperammonemia and progressive dysfunction of multiple organs in patients with propionic acidemia is due to a functional insufficiency of the citric acid (Krebs) cycle with defective production of alpha-ketoglutarate. The basic deficiency of intermediates of the Krebs cycle can decrease production of ATP and explain the low muscle tone, progressive organ dysfunction, and

poor long-term outcome of patients with propionic acidemia.

To test this hypothesis, we will test whether dietary supplementation with alphaketoglutarate precursors (in the form of ornithine alpha ketoglutarate, glutamine or citrate) can improve plasma ammonia and overall outcome in patients with propionic acidemia. In this study, a limited number of patients (3) with propionic acidemia will be given the 3 different nutritional supplements and studied at regular intervals to see whether their glutamine/ glutamate levels improve and if they have fewer episodes of hyperammonemia or acute decompensation. The supplement that produces the best increase in plasma

glutamine levels will be tested for an additional 30 weeks. Children's development and motor skills will be tested before and after therapy to see if there is any improvement. The study will be conducted on outpatients at the University of Utah Clinical Research Center. If the initial trial is successful, we will try to launch a national trial involving multiple centers in the US and abroad to involve the largest number of patients possible.

The current therapy of propionic acidemia is based on restriction of precursors of propionic acid (methionine, valine, isoleucine, threonine, odd chain fatty acids, cholesterol) and administration of carnitine to help remove toxic organic acids. This therapy is not effective in preventing the long-term complications of the disease, even in children identified at birth by newborn screening. This research will test a completely new way of treating patients with severe and disabling metabolic disorders using replacement of downstream products involved in the generation of energy (ATP). This approach, if effective, could be extended to a number of other diseases, including other organic acidemias and mitochondrial disorders.

Could dietary supplementation improve plasma ammonia and overall outcome in patients with propionic acidemia?

Publication Note: The PAF Newsletter is published twice a year. Readers may subscribe by writing to PAF, registering on-line or calling 877-720-2192. Letters and article submissions are welcome for consideration and may be sent to paf@pafoundation.com or mailed to Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us. We are deeply appreciative to Publishers Printing Company for donating the printing costs of the newsletter.

PA FAMILY SPOTLIGHT - AMBER AND TIFFANY BUICE

Hi All.

I wanted to share with you our wonderful wish stories. First off let me introduce my girls. Amber who is 12 and has PA and Tiffany who is 7 and also has PA. We were fortunate enough to experience two wishes. One for each girl. Our first wish was Tiffany's, she wanted to meet Barney. In 2005, the Make-A-Wish foundation sent us to Orlando. The magic started even before we left the Atlanta Airport. We were treated like royalty from then on. We arrived in Orlando to the sight of huge signs and balloons welcoming Tiffany to her wish. We stayed at Disney's Animal Kingdom Lodge. In our room we found stuffed animals, toys, games, and other Disney collectables. We had tickets to every

theme park in Orlando as well as

tickets to anything else we wanted to do. Tiffany got to meet Barney, several times, as well as all the Disney characters. It was an experience that none of us will ever forget.



Tiffany and Amber, Sept. 2005



Amber enjoys the beach!!!

Our second wish trip was Amber's, her wish was to go the beach, sleep in a room, see Mickey again, and fly in an airplane, (some of that came from Tiffany's wish). We were fortunate enough to go to Disney's Vero Beach Resort in Florida. We were greeted with the same gifts as before. Disney does it right!!!! Anything we wanted, all we had to do was ask. We spent a week at the beach and also was able to go back to Orlando to Chef Mickey's, so that Amber could see Mickey again.

As you can see the wish trips were vastly different, but that explains our girls. Both trips were amazing.

We would highly recommend Disney for a wish trip. It is exhausting, but unforgettable.

Take care,

Joey, Sheila, Amber & Tiffany Buice

Lithia Springs, GA

buicejoey@bellsouth.net



Tiffany and Amber enjoy an evening with Chef Donald

PA FUNDRAISING SPOTLIGHT

6th Annual Potluck Dinner to benefit PA, Bath, Maine



Gabrielle Millett (age 8, PA) had a wonderful time at this year's event and was serenaded by a member of the Friends of American Legion during the karaoke portion of the evening. Mom and Dad, Sue & Alex, and brother, Alexander, also helped to plan and coordinate the potluck, live auction and karaoke fundraiser which took place at the Squadron 21 Sons of American Legion hall on April 12, 2008. The benefit raised \$4,892 which was generously donated to Propionic Acidemia Foundation.

Crop-A-Thon for PA, Columbus, Ohio

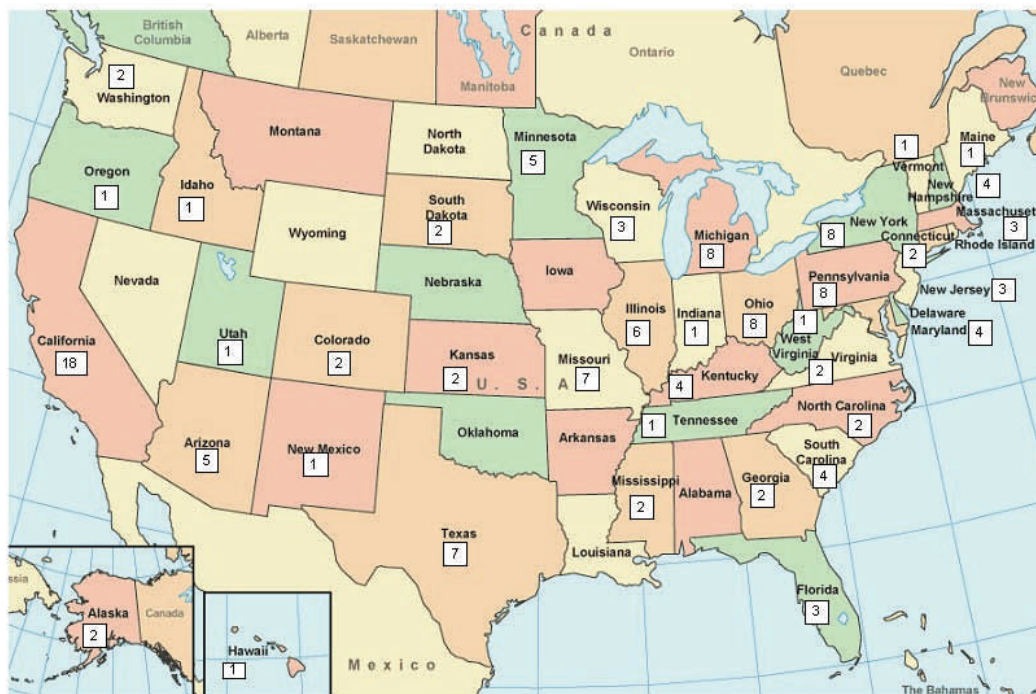
Michelle Ellis (mom to Allison, age 2, PA) hosted a 12 hour scrapbooking event at Archiver's scrapbook store to benefit PAF. Thirty participants made a minimum donation of \$50 to join the event which provided lunch, dinner and door prizes. The total donations accepted for PAF reached \$2950. Go to www.AllisonForACure.com for photos.



PROPIONIC ACIDEMIA FOUNDATION FAMILIES

Since the PAF began offering support services we have become increasingly aware of more families affected by PA. When US families register on the PAF website they are then able to receive our semi-annual newsletter and important information on current research projects. We currently know of 149 affected families in the United States. While we are not able to offer all of our support services at this time to those outside of the US, we have had 49 international families register from 25 different countries, the majority of which are English and Spanish speaking. All families can join our e-mail discussion. A sampling of

137 Known Occurrences of PA in the USA



AROUND THE WORLD

Argentina	3
Australia	2
Bolivia	1
Brazil	3
Canada	6
Chile	2
Ecuador	1
El Salvador	1
Greece	1
India	1
Iran	1
Italy	2
Japan	1
Mexico	1
Norway	1
Panama	2
Saudi Arabia	2
South Korea	1
South Africa	6
Spain	1
The Netherlands	1
UK	6

You can register with PAF at www.pafoundation.com or update your contact information by e-mail paf@pafoundation.com.

DNA SAMPLES ARE NEEDED FOR THE PAF/CORIELL PATIENT REPOSITORY

Creation of the Registry

2007 was a special year when PAF and Coriell Institute announced the creation of a long-awaited DNA Repository. This project is unique because PAF and Coriell are collaborating to obtain DNA samples from PA patients, parents and extended family members in addition to collecting clinical data. Coriell Institute will store the DNA samples at its cell and DNA repository to maintain a PA collection for researchers to access for molecular biological studies. PAF, with the help of its Medical Advisory Board, has developed a questionnaire for the PA families wishing to donate samples which will provide useful information to clinicians and researchers who may want to do comparative studies. All information in the questionnaire is strictly confidential and the identities of the patients are protected by a coding system. In this way, PAF will be able to contact families in the future, if they so desire, to broaden the data in the registry.

Why is the Registry Needed?

We are hopeful that more families and doctors will assist in adding to the DNA repository as this is a valuable resource for research.

Having an on-going "living" registry not only provides a unique DNA collection for researchers, but will benefit clinicians trying to determine the course of secondary medical issues that PA patients can develop over time. Long QT, cardiomyopathy, pancreatitis, optic nerve atrophy and osteoporosis are examples of

some conditions that researchers and clinicians would like to understand better in PA patients, and to determine why some patients acquire them and others do not. Diet and medications also vary greatly between PA patients, and the knowledge gained from the PA family questionnaire may help medical personnel better understand how these factors influence a patient's well-being and long-term management.

Where's the Mutation?

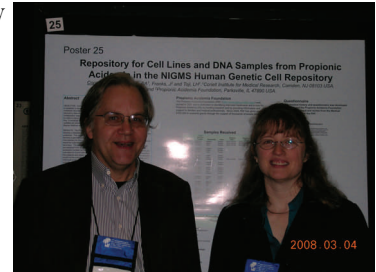
The final aspect of the PA registry that PAF would like to promote is the **genotyping** of the samples collected. Some PA patients have already had their mutation(s) analyzed and know whether PCCA or PCCB (or both) is affected in their family. This information is extremely useful and is a gold mine for researchers who want to correlate PA mutations with the course of the disease over a lifetime. Coriell would also like to add this information to their website to enhance

the usefulness of the registry to attract researchers. PAF would like to see as many families take advantage of this technology as possible to determine your child's specific mutation(s) to add to the registry.

How do I Participate?

PAF will mail a DNA sampling kit with instructions to any family or doctor who requests one. It's easy! Take the kit to your metabolic physician or pediatrician and ask for the additional blood draw.

When you wish to have your child's specific mutation(s) determined, please contact PAF for a list of labs. The DNA analysis may take a few months to complete, but knowing where your child's mutation lies will benefit the scientific community and eventually allow researchers to correlate PA disease characteristics with specific mutations.



DONALD COPPOCK, PH.D (CORIELL INSTITUTE FOR MEDICAL RESEARCH) AND JILL FRANKS (PAF) AT THE SIMD POSTER SESSION

2008 FELLOWSHIP GRANT

Propionic Acidemia Foundation (PAF) and the National Urea Cycle Disorders Foundation (NUCDF) announce our partnership in hope by providing a jointly-funded, post doctoral Fellowship Grant. This collaborative effort seeks to improve the quality of care of affected individuals by attracting promising new investigators with interest in biochemical genetics to the field of urea cycle and propionic acidemia disorders. The goal of the fellowship is to help support postdoctoral fellows who specialize and focus on research, clinical treatment and coordination of multidisciplinary care of UCD and PA in the United States, while advancing understanding, early detection, treatment and therapeutic approaches for the disorders.

For more information, please visit www.pafoundation.com.



Cindy LeMons (NUCDF) and Jill Franks (PAF) exhibit at SIMD.

HOW YOU CAN HELP



You can now raise money for Propionic Acidemia Foundation (PAF) by shopping at Dominicks, Safeway and other grocery store chains. Once your grocery loyalty card is linked to PAF through the eScrip program PAF will receive a portion of the proceeds from your purchases. You can also link you credit and/or debit cards to your eScrip account, so that more can be raised while you do your everyday shopping.

It is easy to sign-up:

1. Log on to www.escrip.com and go to “sign up”.
2. Designate PAF to receive contributions by searching on Propionic or entering our ID # 500017726.
3. Register your grocery club cards from a participating merchant like Dominicks/ Safeway— and your debit, ATM and credit cards if you wish.

Other online fundraising efforts:



Raised \$168.09



iGive.com
Change online shopping for good.

Raised \$1375.77



Raised \$333.85

Help Us Find the Cure!

Name _____

Please send an acknowledgement to:

Address _____

Name _____

City _____ State _____

Address _____

Zip code: _____

City, State, Zip _____

Phone: _____

E-mail _____

Enclosed is my contribution of \$ _____ in honor of/in memory of _____

If you work for a company that has a matching program, please include the matching form.

Please mail your check made payable to:

Propionic Acidemia Foundation

1963 McCraren Road

Highland Park, IL 60035

Thank you for making a difference.

SEARCHING FOR A CURE
HOPE FOR OUR CHILDREN

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We would like to thank our Medical Advisory board for all of their support, input, advice, and knowledge. We could not do it without you.

We would like to thank James Leonard, PhD for his advice and support on the MAB and wish him the best in future endeavors.

We would like to acknowledge and thank each of you personally for making a difference for families affected by Propionic Acidemia.

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