SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 7 AUTUMN 2009

Climbing For A Cure

They made it! On July 5, 2009 Michelle (Jacqueline) Burns and Shawna Macnamara began their ascent to the 14,410 ft. Mt. Rainier. Just a couple hours from Seattle, Washington, it's the highest volcano in the United States. Mt. Rainier is the most heavily glaciated peak in the US, outside of Alaska, and it is the North American training ground for the world's tallest peaks. Along with their team they successfully summited Mt. Rainier at 7 a.m. on Thursday July 9, 2009. From Michelle (Jacq), "We hit the ground running at 1:15 a.m. and watched the sunrise as we climbed. It was a beautiful morning and a climb that we will never forget. Thanks so much for all of your cheers and support."

Why they're climbing. On January 7th, 1999 Trent and Jacq's daughter, Kaitlin Blake Burns, was born looking healthy and happy. In less than 24 hours things went terribly wrong. Kaitlin became very sick and was diagnosed with Propionic Acidemia. Jacq called Shawna from the hospital and asked her to pray…Shawna doesn't normally get out of bed in the middle of the night to say prayers but in this case, she did. Shawna has been a friend to Kaitlin for so many years and it's fitting they're trekking in her honor. Children with this disease can often find a short flight of stairs daunting and climbing a mountain is virtually impossible. Shawna wishes they could be able to do what she and Jacq are attempting and are hoping that they can make a difference.

Join their cause and see photos! So far they have they raised over $10,000 and are still climbing! For photos you can join their Facebook group "Climbing For A Cure" and you can donate to their campaign at www.firstgiving.com/climbingrainierforacure.

Michelle Burns and Shawna Macnamara at the summit of Mt. Rainier (14,410 ft.).

In Memory of Logan L. Laack

August 2, 1989 – August 27, 2009

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INSIDE

MISSION: The Propionic Acidemia Foundation is dedicated to finding improved treatments and a cure for Propionic Acidemia by funding research and providing information and support to families and medical professionals.

VISION: To create a future where Propionic Acidemia can be prevented and any affected individual can be cured and live a productive life.

PA FAMILY SURVEY REQUEST

Survey of health status and complications among propionic acidemia patients registered with the Propionic Acidemia Foundation

Dear PAF members,

My name is Loren Pena and I am a faculty member in clinical genetics in the Department of Pediatrics at the University of Illinois at Chicago. I would like to invite your participation in a study that I am conducting with Dr. Barbara Burton at Children's Memorial Hospital titled "Survey of health status and complications among propionic acidemia patients registered with the Propionic Acidemia Foundation." The purpose of the study is to gather clinical information about the health of patients with propionic acidemia (PA) that are registered with the Propionic Acidemia Foundation (PAF).

I have found that published information regarding PA consists mainly of case reports with only one patient or a limited number of patients. It is therefore difficult to determine how commonly complications occur among patients with PA. With the aid of a survey and the members of the PAF, I would be able to collect clinical information from a large sample of patients with PA. This information would improve our understanding of how patients with PA are doing.

You can participate if you are affected with PA or have a family member who is/was affected with propionic acidemia. We are interested in information on both living and deceased patients. Participation is voluntary, involves minimal risk, and will consist of filling out a questionnaire that will be distributed with the help of the PAF through the email distribution list and on the PAF website. We ask that a parent or guardian fill out the questionnaire with information about the person with PA. However, if you are affected with PA and live independently, we ask that you fill out the survey for yourself. You are indicating your consent to participate in the study by filling out the questionnaire.

The survey includes a wide range of questions about birth history, diagnosis, and complications related to PA and will take approximately 30-45 minutes to complete. We ask for the affected person's name and date of birth in the questionnaire and the name and contact information of the person filling out the form in case we need to re-contact you (with your permission) regarding the answers. However, the information provided in the questionnaire will be maintained confidentially by deleting the participant's name, date of birth, and contact information from the completed survey and maintaining this information separately from the surveys. Only Dr. Pena and Dr. Burton will have access to the study data, which will be kept in a password-protected computer and locked office on the UIC campus. There is no cost or compensation associated with the study, and you can withdraw your participation by contacting Loren Pena if you change your mind after submitting a questionnaire. Although there are no direct benefits to your participation, the medical community will benefit from the information that we glean from the study as we continue to learn about the health concerns, complications, and life history of patients with PA.

If you have any questions, please feel free to contact me by email at lpena@uic.edu or by mail addressed to me at The University of Illinois at Chicago, Department of Pediatrics, Division of Genetics, MC 856, 840 South Wood Street, 12th floor, Chicago IL 60612. If you have any questions about your rights as a research subject or concerns, or complaints, you may call the Office for the Protection of Research Subjects (OPRS) at UIC at 312-996-1711.

The questionnaire will be mailed in a separate mailing to clinics and families.

For an exact copy of this advertisement containing the IRB stamp with IRB approval dates, please go to www.pafoundation.com.

PAF is compiling a Family Directory that will be distributed to PAF families. If you would like to have your family information included in the Directory, please contact Propionic Acidemia Foundation for a form.

N-CARBAMYLGLUTAMATE STUDY UPDATE

Nicholas Ah Mew, MD FRCP(C), Biochemical Genetics Fellow, Children's National Medical Center

The N-Carbamylglutamate study is performed at Children's National Medical Center in Washington DC and at Children's Hospital of Philadelphia, by a team led by Drs. Mendel Tuchman and Marc Yudkoff. The purpose of this study is to investigate whether N-Carbamylglutamate (NCG, Carbaglu) can improve urea cycle function and decrease blood ammonia in individuals with propionic acidemia, methylmalonic acidemia as well as urea cycle disorders such as NAGS, CPSI, and OTC deficiency.

To date, 7 patients with propionic acidemia and one patient with methylmalonic acidemia have participated in our study, bringing our total enrollment to 15 patients. Our goal is to enroll a total of 14 patients with each condition. Our interim analysis demonstrates that:

- Participants with NAGS deficiency showed normalization of urea cycle function and ammonia after treatment with N-Carbamylglutamate.
- Participants with propionic or methylmalonic acidemia showed improvement of ammonia, urea cycle function, and amino acids, but to a lesser degree than patients with NAGS deficiency.

Plans for 2010-2011 include enrolling further participants in this trial and developing a long-term trial of treatment with N-Carbamylglutamate in patients with propionic and methylmalonic acidemia. We also intend to publish our current results from our cohort of propionic acidemia patients.

For more information about this study please contact PAF at 1-877-720-2192 or paf@pafoundation.com.

CORIELL QUESTIONAIRE & CONSENT FORMS EN ESPANOL

Coriell Questionnaire and Consent Forms now available in Spanish!

The Propionic Acidemia Foundation and Coriell Institute for Medical Research are collaborating to build a PA DNA collection at NIGMS Human Genetic Cell Repository. In 2007 PAF began collecting DNA samples from PA patients and family members to generate a DNA collection large enough for researchers to be able to use as a comparative tool in research projects. The goal of providing samples is to improve the understanding of PA. For example if enough samples are submitted researchers may finally begin to correlate the numerous characteristics seen in PA patients with specific mutations. Secondary conditions and long-term complications of PA may also be correlated to specific mutations in the future and we may understand why certain patients develop pancreatitis or cardiomyopathy and others do not. PAF will follow-up with patients every few years to create a database on patient status plus new scientific and clinical information obtained from researchers. Currently we have one PAF-funded researcher, Dr. Kimberly Chapman, who is already making use of this PA DNA sample collection.

To aid in our understanding of the disease PAF, along with its Medical Advisory Board, has developed a questionnaire and consent form that families need to fill out when they submit their samples. *These forms are now available in Spanish!* PAF and Coriell have an IRB approved protocol for sample submission and for recontacting families in the future. The ability to stay connected to the families who have provided samples is important so that PA patients can be followed as the course of the disease continues. We value your privacy as we do our own, so to protect the identity of patients and their families, only PAF is able to connect the identity of the subject with the DNA sample in the Repository. This information will not be shared with Coriell.

Please help us make this project a success by contacting PAF to request a sample kit. The kit will include a consent form and questionnaire. Our hope is that each affected individual and their immediate family members will donate samples to build this DNA repository. To order a kit, or if you have questions please contact PAF at 877-720-2192 or paf@pafoundation.com

PA Family Day: Better Than Ever

Jordan & Ryan at PA Family Day

My family and I attended PA family day on July 25, 2009 in Burlington, Kentucky. I am 12 years old and my brother, Jordan, has PA and is nine years old. Eight families, friends and relatives attended from the states of Texas, Ohio, Kentucky, Georgia, and Illinois.

Although PA family day had a bad start, due to rain, it was a nice opportunity to meet all the families and interact with each other before everyone ran off to do their thing. Fortunately, the rain cleared up around lunch, which by itself was amazing.

Then we went on a hay ride. But of course, not just any hay ride, but a hay ride that literally went up the side of a mountain. It was very scenic. To make things better, on the hay ride we stopped in an old historic town called Rabbit Hash, where we got to look at the antique stores, an old fashioned general store and the hundred-year old gas pumps. It was amazing.

When we got back, the kids basically just hung around and played while the adults had a board meeting. Some people swam in the pool. After maybe an hour or so, we got to ride in dune buggies on their farm which was also really fun.

After family day ended, we still had the rest of the evening before we left. In that time, I got to play with Talli, Amber, Tiffany, and Lucy at the hotel. We played golf and I got to go swimming. When it was time to leave, we stopped at an ice cream place for a snack. PA family day was awesome. I can't wait until next year.

Ryan, age 12 (Jordan's brother) Highland Park, IL

Publication Note: The PAF Newsletter *is published twice a year. Readers may subscribe by writing to PAF, registering online 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.*

RESEARCH STUDIES IN PROPIONIC ACIDEMIA

Dr. Jan Kraus' laboratory, Dept. of Pediatrics, University of Colorado School of Medicine

Propionic acidemia (PA) is a serious life threatening inherited disorder of metabolism. The disease is caused by deficiency of an enzyme called Propionyl CoA Carboxylase or PCC for short. PCC is a large enzyme consisting of six alpha and six beta subunits. The enzyme deficiency in turn is caused by mutations in either the PCCA or PCCB gene. The PCCA or PCCB gene is essentially a stretch of DNA that contains all the information for cells in an individual to make the alpha or beta subunit, respectively, of the enzyme. My laboratory works on two projects associated with propionic acidemia. The aim of the first project is to solve the three dimensional structure of the enzyme using crystallization and X-ray diffraction. Why is this important? Solving the structure of the enzyme is essential for at least two reasons: first, the structure would allow predicting the impact of each mutation on the function of the enzyme; second, any meaningful design of treatment drugs should be based on the enzyme's structure. We are working on this project in collaboration with Dr. Vivien Yee who is an expert crystallographer and is based at the Case Western University in Cincinnati.

Our second project deals with determination of the DNA mutations causing PA and how these mutations correlate with the course of the disease in patients with PA. We have been involved in a large international study of 56 European patients with PA. We aim to improve treatment and clinical outcomes by correlating their particular PCC mutations with the clinical course of their disease. Defining PCC mutations will improve newborn screening and help affected families to ascertain which family members may be carriers. Also, in the future there will be treatments that will be tailored to particular mutations so knowing what the mutations are in the family will be important. We hope to finish this international study by the end of 2009 and will then start on a similar study of US patients and PAF members.

I am very grateful for the support I have been getting from the PAF foundation to carry out this research and I hope that our work will lead to a treatment that will clinically benefit a number of PA patients in the future.

MAYO CLINIC STUDY UPDATE

Dr. Mike Barry's laboratory, Mayo Clinic Rochester

We have been testing gene therapy in a mouse model of propionic acidemia where both PCCA genes have been deleted and the animals die within 36 hours of birth. Our work has demonstrated that we can treat the disease, but that the effects are only temporary in this stringent model, in part because one cannot use conventional PA treatments that temper the disease.

To circumvent these problems and move closer to clinic, we are currently 1) making improved mouse models of PA and 2) are improving the efficiency of the gene therapy treatment. To improve the mouse models, we are generating mice that will express mutations in the PCCA gene that are identical to those that have been observed in patients. These mice will hopefully provide a better model for gene therapy by having partial PCC activity like some known PA patients. The improved PA mouse models may better mimic human propionic acidemia and better show how the new PCCA genes affect the host after the therapy. To improve gene therapy efficacy, we are genetically re-engineering the PCCA protein itself to amplify the amount of protein that can be produced and to increase the amount of protein that is delivered into the mitochondria where it is needed.

GENE EXPRESSION IN PATIENTS WITH PA AND THEIR CARRIER PARENTS

Dr. Kimberly Chapman's laboratory, University of Pennsylvania

I examine cells from people with propionic acidemia (PA), their parents and presumably "healthy" people to identify their differences and similarities. I hope these studies lead to a better understanding of the impact on other cellular functions of a block at the propionyl CoA carboxylase enzyme (PCC). These previously under-recognized targets of a PCC defect may provide new treatments and complication prevention strategies in PA.

To do this, I used cells from the Corriell Institute for Medical Research that were donated from families with PA (through the work of the PA foundation). I then assayed these cells for their level of RNA. RNA is the intermediate step between DNA (the genetic code material) and protein (which is the major building block of cells, as well as make-up enzymes). Cells from patients with PA have different amounts of RNA compared to" healthy" people for about 400 genes (out of the 30,000 genes assayed). Cells from their parent(s) also have different levels of RNA as compared to that from "healthy" people for about 480 genes. Some of these genes regulate cell cycle and are involved in immune response. Presently I am confirming these results and identifying targets for further analyses.

PAF FUNDRAISING SPOTLIGHT

Past Events and Campaigns

- **9/09** 4th Annual Tailgate Party & Corn Hole Tournament for PA, raised over $15,000, Gahanna, OH
- **9/09** Ready, Set, Grow Carwash, raised over $1100, New Albany, OH
- **9/09** Jewel-Osco Shop and Share - raised $79
- **7/09** Climbing Rainer A Cure, currently raised over $10,000, Seattle, WA
- **6/09** Corn Hole Tournament for PA, raised $2800, Pomeroy, OH
- **6/09** Neighborhood Beautification Day, raised $2200, New Albany, OH
- **5/09** Poker Run for PA, raised over $1500, Columbus, OH
- **5/09** Dublin Jerome High School Pancake Dinner, raised $400, Dublin, OH
- **Ongoing**- Cans for a Cure, raised an additional $2000 for recycling cans and bottles, Sandy McKillop, NY

Fundraise online by doing what you already do!

- **NEW "**Club Bing", clubbing.com - play games and donate tickets to PAF.
- Search the internet through GoodSearch.com
- Shop through GoodBuy.com
- Search or shop through iGive.com
- Sign up for eScrip at http://escrip.com/
- Sell items on Ebay using MissionFish. You pick what percentage goes to PAF.

Join and follow Propionic Acidemia causes on Facebook:

- "Propionic Acidemia Foundation"
- "Climbing For A Cure"

Or online at:

- GwenForACure.com
- Firstgiving.com/climbingrainierforacure

IN MEMORY OF LOGAN

www.caringbridge.org/la/logan

Logan L. Laack
8/2/89 - 8/27/09
An inspiration to all.
He chose to live an awesome life.

A parent's love for a child is ageless.

ANNUAL REPORT: PAF AUGUST 1, 2008– JULY 31, 2009

FINANCIAL REPORT

Revenue:

Contributions:	$97,729
Interest Income:	$1,356
In Kind Donations:	$4,387
Total Revenue:	$103,472

Expenses

Research Grants/Exp	$79,390
Programs and Outreach	$1,585
Fundraising	$70
Operations	$2,341
Total Expenses:	$83,386

Cash Assets: 8/1/2008	$66,872
Cash Assets: 7/31/2009	$82,570

BOARD OF DIRECTORS/OFFICERS

Jill Chertow Franks, President
Brittany Smith, Secretary, Treasurer
Janice S. Boecker
Jennifer Mouat
Michael Rosenson

Board disclosure: Jill Chertow Franks is the sister-in-law of Michael Rosenson.

Donations made by board members totaled $1088.

PROGRAM ACCOMPLISHMENTS

Research: 3 samples from affected individuals and 2 from carriers were submitted to the DNA Repository at Coriell Institute for Medical Research in Camden, NJ.

Grant Disbursements:

- $30,000- Jan P Kraus, Ph.D., University of Colorado at Denver and Health sciences Center (UCDHSC) Denver, CO: "Crystallization and structure determination of human propionyl-CoA carboxylase"
- $20,000 - Jan P. Kraus, Ph.D., UCDHSC Denver, CO: "Genotype –phenotype correlations in PA"
- $29,381- Kimberly Chapman, MD, Ph.D., Children's Hospital of Philadelphia, Philadelphia, PA: "Gene Expression Profiles of Patients with Propionic Acidemia and their Carrier Parents"

OUTREACH:

PA Family Day: This year's event was held in Burlington, KY. We were thrilled to have 8 families in attendance affected by PA from Georgia, Illinois, Kentucky, Ohio, and Texas.

Newsletters: We published and distributed 2 newsletters this year to affected families, clinicians, and donors.

Help Us Find the Cure!

*Name*_____

*Address*_____

City, State, Zip _____

*Phone*_____

*E-mail*_____

Please send an acknowledgement to:

*Name*_____

*Address*_____

*City, State, Zip*_____

*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, Highland Park, IL 60035

Thank you for making a difference.

Searching for a Cure
Hope for Our Children

Propionic Acidemia Foundation
1963 McCraren Rd.
Highland Park, IL. 60035

Phone: 1-877-720-2192 toll free
Fax: 1-877-720-2192
E-mail: paf@pafoundation.com
Website: www.pafoundation.com

Propionic Acidemia Foundation

Thank you Publishers Printing Company for contributing the printing and mailing of the PAF Newsletters.

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

Propionic Acidemia Foundation is run 100% by volunteers and we couldn't do it without you.