Fall 2022

PROPIONIC ACIDEMIA FOUNDATION

Searching for a Cure Hope for Our Children

Land of the Free, Home of the Brave Conference Update

Dr. Gerard Berry receives Award of Excellence from PAF and OAA

Land of the Free, Home of the Brave, a collaborative patient/family conference between the Propionic Acidemia Foundation (PAF), HCU Network America, and Organic Acidemia Association took place in Bethesda, Maryland on June 25-26, 2022. This was PAF's first conference with the OAA and HCU.

The primary objective of the conference was sharing scientifically backed information regarding best practices and research to effectively manage Organic Acidemias and Homocystinurias. This was achieved through patients and caregivers sharing their experiences, healthcare professional's presentations, breakout sessions led by healthcare professionals, industry and research organizations sharing information on research underway and opportunities for new therapies in the future.

The second goal of our conference was to bolster the conversation between patients, caregivers and family members. Providing an opportunity for them to socialize, exchange information and tips, in hopes that they realize they are not alone in this journey.

Land of the Free, Home of the Brave brought together 47 industry leaders, 28 medical professionals and 149 patients, caregivers and relatives from all over including more than 5 countries!

PA Registry

Help move research forward for propionic acidemia. Participate in the Propionic Acidemia International Registry.

As of August 31, there are 116 participants.

For more information on joining the registry, or to update your information, go to www.paregistry.org.

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.

EITHAN'S STORY

Eithan Arana, edad: 2 años, ciudadanía ecuatoriana con padres casados un hermano mayor de cinco años, eithan con diagnóstico de acidemia propiónica. Nuestra historia comenzó un 18 de abril 2021 cuando eithan tenía 9 meses de edad presento su primer síntoma que fue convulsiones focalizadas en pie derecho permaneció ingresado por 6 días en el hospital pediátrico incluyendo dos días en cuidados intermedios durante su estadía realizaron laboratorios la mayoría en sus parámetros normales excepto la resonancia magnética que salió alterada con un posible diagnóstico de enfermedad metabólica, luego varios tratantes de pediatría tenían diferentes diagnósticos diferenciales uno de ellos era la epilepsia congénita, por lo cual sale de alta solo con medicina para epilepsias, eithan después de su egreso del hospital queda hipotónico, pediatra genetista envía tamizaje metabólico ampliado fuera del país donde no está claro el diagnóstico y decide enviar una prueba genética a eeuu saliendo como resultado positivo para acidemia propiónica con variantes en el pccb desde el 15 de julio del 2021 comienza está dura lucha en nuestro país por no contar con especialidades a fin a su patología tampoco se cuenta con sus fórmulas especiales y su medicina por no ser una enfermedad que se encuentra en el cie 10 de nuestro país ningún seguro cubre patología todo es por gastos propios, eithan iba perdiendo peso hasta llegar un punto que parecía un niño caquéxico por desesperación comencé a preguntar en otros países como podría ayudar a mi hijo , hasta que gracias a Dios conocí a las fundaciones de estados unidos en el cual me han venido ayudando a conseguir a doctores especialistas, nutricionistas además con sus fórmulas mediante los integrantes así tenemos un año en lucha constante batallando con esta enfermedad , en nuestros país estamos luchando constantemente en reuniones con las autoridades nacionales de salud para que la patología entre en la codificación de nuestras enfermedades raras que tiene el ecuador ya que a nivel nacional los médicos y nutricionistas que hemos visitados no tienen conocimientos de lo que es acidemia propiónica siendo los hospitales más grandes públicos y privados del ecuador por tal motivo es mi lucha constante ingresar la acidemia propiónica para poder ayudar a mi hijo y a los demás niños que padezcan esta enfermedad en mi país porque es muy difícil y estresante lidiar con esta situación.

han fallados mis intentos en varias ocasiones, hemos viajado 8 horas desde nuestras casa a la capital del ecuador para papeles burocráticos pero no perdemos la esperanza ,en ecuador estamos con una pediatra general y una gastroenteróloga que le han puesto muchas ganas a eithan con la ayuda e indicaciones de los médicos extranjeros siguiendo los protocolos de eeuu ellas chequean a eithan para su crecimiento, en la actualidad nos abastecemos de su fórmula con las donaciones de los padres de las fundaciones hasta hacer realidad que nos tomen en cuenta en mi país ya que no contamos con sus fórmulas tampoco con sus exámenes de aminoácidos dichos exámenes se envían Alemania demoran alrededor de 2 meses en entregarnos los resultados y es por medio de un laboratorio privado que tiene convenio con dicho país, tampoco contamos con nutricionistas especialistas en acidemia propiónica incluso cuando eithan está enfermo y debemos cambiar su fórmula no lo hacemos , solo se aumenta azucares en sus bebidas gracias a los consejos de los padres de la fundación. Recién tenemos un equipo metabólico de Tampa que nos ayudara con sus cambios de formulas hemos sido muy bendecidos por Dios por encontrar muchas personas ayudándonos,

En la actualidad con mucha fe en Dios eithan ya logra caminar, entiende ordenes, come solo, si está atrasado en el habla, no logra hablar, tiene bajo peso, pero lo mas importante es un niño feliz, mi meta es ayudar a más niños del ecuador, así como otros papitos me han ayudado si no fueran por ellos estuviera perdida.

PA Zoom Chat in Spanish

Thank you Jill Chertow and Frances Torres for setting up the Propionic Acidemia Foundation Zoom meeting in Spanish! It was phenomenal meeting other parents from Argentina, Costa Rica, Panama, and Ecuador! It was great connecting with other parents that understand your battle with PA. Thank you moms and dads that participated and gave hope to the new parents that joined the chat! It was wonderful advice that was given from one another and it was wonderful meeting everyone!

Gracias Jill Chertow y Frances Torres por organizar la reunión de Zoom de la Fundación de Acidemia Propiónica en español! ¡Fue fenomenal conocer a otros padres de Argentina, Costa Rica, Panamá y Ecuador! Fue genial conectarse con otros padres que entienden la batalla con PA. ¡Gracias mamás y papás que participaron y dieron esperanza a los nuevos padres que se unieron al chat! ¡Fueron maravillosos los consejos que se dieron unos a otros y fue maravilloso conocerlos a todos!

Mindfullness with Bryan

Bryan Kelly, Certified Meditation and Mindfulness Teacher

For those of you who don't know me, I am Bryan Kelly, 36 years old with PA. I am certified in mindfulness and meditation. Being more mindful has significantly improved my life by limiting my stress, focusing on what I can control and just overall enjoying life.

Here are 10 ways you can start being mindful today.

1. Simply breathing - I do this multiple times a day. Just take a few moments to get connected with your breath. You can do this standing, sitting or lying down.

2. Show gratitude - every morning when I wake up I step outside and say thank you for everything that has been given to me.

3. Mindful walking - If only for ten minutes taking a walk and being mindful of the animals, flowers and everything nature has to offer is really calming.

4. Journaling/Poetry - Getting my thoughts down on paper has been a great way to get those inner feelings out.

5. Yoga - Yoga has done absolute wonders for me and it can for you. There are thousands of videos on YouTube. Just a few poses a day will greatly increase your mood.

6. Mindful eating - When you sit down to eat, focus on the feel and smell of the food first, then slowly eat and enjoy every bite. Fully focus on the food.

7. Listening to music - What you listen to matters. Since everything gets programmed into the subconscious. I often prefer songs without lyrics. Putting on some peaceful music and bringing your full attention to it is a great way to be enjoying the moment,

8. Playing an instrument - I now have numerous instruments that I play such as singing bowls, flute and drums. Sometimes it's for a half hour or only ten minutes, either way it's a great way to zen out.

9. Gardening - Something about growing my own plants and food is extremely satisfying. Taking care of them, watching them grow, not to mention the end product is always delicious.

10. Reading - I was never a big reader until very recently. Now reading is one of my favorite ways to enjoy the moment.

There are thousands of ways you can practice mindfulness. The above are some of the techniques I use in my life. If you're interested in learning more about mindfulness meditation or joining my 11:11. meditation's email me at Bepresentlifestyle@gmail.com or visit my website at Bepresentlifestyle.com

Warriors Birthday Club

This year birthday cards will be made by students at Oak Lawn-Hometown Middle School and St. Linus for participating families. We are thankful they have volunteered to do it again this school year. Please sign up a patient or sibling for the Warriors Birthday Club at http://www.pafoundation.com/warriors-birthday-club/.

If you signed up last year, you will need to sign up again, so we have current information.

We want to hear from you!

Have a PA story to tell, event to promote or news?

Spring newsletter submissions due by February 1, 2023.

PAF AWARDS $50,000 CONTINUATION GRANT

CHEMICAL CHAPERONE TREATMENT TO RESTORE ENZYME ACTIVITY IN FOLDING MUTATIONS OF PROPIONYL CO-A CARBOXYLASE: TOWARDS A PERSONALIZED THERAPEUTIC STRATEGY IN PROPIONIC ACIDEMIA (PA).

Kenneth N Maclean PhD
Professor of Pediatrics
Ehst-Hummel-Kaufmann Family Endowed Chair in
Inherited Metabolic Disease
University of Colorado School of Medicine

Propionic acidemia (PA) is a severe life-threatening disease for which there is currently no truly effective treatment. The disease is caused by mutation in one of the two genes that code for the enzyme propionyl-CoA carboxylase (PCC). This enzyme is made up of two different proteins that fold around each other into a complex structure with six of each of these two molecules. This is a very unusual and complex structure for a metabolic enzyme. A number of mutations in PCC cause PA by interfering with the ability of the PCC enzyme to fold and assemble correctly thus destroying the enzyme's function. In our previous years funding, we identified a range of chemicals that act as chaperones and restore mutant PCC folding and function in a bacterial expression system. In our present funding period, we are investigating the potential therapeutic potential of this approach using both purified mutant PCC protein and human PA patient derived cells. Additional studies are directed towards investigating if the accumulation of misfolded mutant PCC within the cell is a possible pathogenic mechanism in PA. We hope our investigations will shed new light on pathogenesis in PA and provide a rational basis for a possible mutation-specific therapeutic strategy for this disease. We remain very grateful to the PA foundation for funding this work.

PAF FUNDED RESEARCH UPDATE

LEARNING FROM MOUSE MODEL OF METABOLIC CHANGES IN PROPIONIC ACIDEMIA

Guo-Fang Zhang
Department of Medicine, Division of Endocrinology, Metabolism Nutrition, Duke University Medical Center, Duke Molecular Physiology Institute, Durham, NC 27701, USA

Pcca-/-(A138T) mouse - an animal model of propionic acidemia (PA)

Propionyl-CoA carboxylase (PCC) is an essential enzyme. Not like many other gene manipulations, the complete deletion of PCC is lethal to mice. Dr. Michael Barry's group created a mouse model (Pcca-/-(A138T) mouse) of PA by introducing human mutated Pcca to mice after mice Pcca is deleted (Guenzel et al., 2013). Pcca -/-(A138T) mouse can survive to adult for research purpose with low PCC acidity in most organs except in muscles including heart and manifests some similar symptoms of PA.

Altered acylcarnitines profile in Pcca-/-(A138T) mouse

Like in PA patients, propionylcarnitine is elevated in Pcca-/-(A138T) mouse plasma (He et al., 2021). In tissues, propionylcarnitine accumulation negatively corresponds to the residual activity of PCC. The increase of propionylcarnitine in Pcca-/-(A138T) mouse is the highest in lung, liver, and white adipose tissue (> 10 folds) where PCC activity is the lowest. Other organs show mild increase of propionylcarnitine (≤5 folds) because of relatively higher residual PCC activity. The massive accumulation of propionylcarnitine in lung and liver traps l-carnitine and reduces all other acylcarnitines. The l-carnitine trapping in liver and lung could inhibit fatty acid oxidation (Wang et al., 2018). The interrupted fatty acid oxidation in liver is evidenced by the decreased acylcarnitines and ketone body (3-hydroxybutyrate) under fed status. The reduced acetylcarnitine in lung and liver of Pcca-/-(A138T) mouse implies the decreased mitochondrial acetyl-CoA, which might explain 18-30% reduction of citrate (TCA cycle intermediate) in both organs. High propionyl-CoA in both lung and liver also competes acetyl-CoA in citrate synthesis and leads to citrate reduction and an increase of methylcitrate which is not a TCA cycle intermediate. Acylcarnitine data from Pcca-/-(A138T) mouse organs demonstrates that severity of metabolic disturbance/complication in PA is determined by the residual activity of PCC.

The relative contribution of propionyl-CoA anaplerosis to TCA cycle in organs

Tricarboxylic acid (TCA) cycle plays important roles in energy production and anabolism. Anaplerosis is a metabolic process that TCA cycle intermediates are replenished after they leave cycle for anabolism. Propionyl-CoA, like many other metabolic substrates, is a good anaplerotic substrate. Relative anaplerotic flux of propionyl-CoA over total TCA cycle turnover is in the following order (from high to low) among organs, liver = skeletal muscle > white adipose tissue > pancreas > lung > kidney > brain > brown adipose tissue > heart. The low relative propionyl-CoA anaplerosis in heart and brown adipose tissues is ascribed to high TCA cycle turnover to meet organs' energy demands. The high anabolism in skeletal muscle (high efflux of amino acids), liver (glucose and fatty acid synthesis), white adipose tissue (fatty acid synthesis) requires high anaplerosis from propionyl-CoA and other anaplerotic substrates. The low PCC activity impedes propionyl-CoA analperlosis in lung, liver, kidney, brain, and white adipose tissue of Pcca-/-(A138T)

Learning from mouse model Continued...

mouse and could affect the metabolism of macronutrients, like glucose and fatty acids.

The altered lipid composition in Pcca-/-(A138T) mouse

The accumulation of propionyl-CoA not only interrupts the above metabolic activities but also modifies lipid compositions. Propionyl-CoA, analog of acetyl-CoA, can participate in fatty acid synthesis and fatty acid elongation which makes odd-chain fatty acids. Odd-chain fatty acids in lipids go up to ~10% in Pcca-/-(A138T) mouse with chow diet. The high odd-chain fatty acid synthesis from propionyl-CoA could decrease even-chain fatty acid synthesis, which is also observed in PA patients. The breakdown of odd-chain fatty acids generates more propionyl-CoA during the fasting or endurance exercise. The altered macronutrients metabolism and high odd-chain fatty acids in Pcca-/-(A138T) mouse might explain why PA patients should avoid long-time fasting and endurance exercise. The effect of increasing odd-chain fatty acids in lipid on lipid membrane function is not clear and warrants further investigation.

Propionyl-CoA-genic amino acids in Pcca-/-(A138T) mouse

PA patients follow protein restriction or modified protein diet to reduce the intake of four propionyl-CoA-genic amino acids, i.e., valine, isoleucine, threonine, and methionine. Propionyl-CoA accumulation and altered fuel metabolism in Pcca-/-(A138T) mouse could affect amino acid metabolism including the above four propionyl-CoA-genic amino acids. With chow diet, threonine and methionine are increased in all measured organs (brain, heart, lung, liver, kidney, quad, gastroc, white adipose, and brown adipose) of Pcca-/-(A138T) mouse. However, valine and isoleucine, two branched-chain amino acids, are not dramatically different compared to wild type mice. Propionyl-CoA accumulation is expected to inhibit the metabolism of propionyl-CoA precursors and to increase their levels, like methionine and threonine. However, the increment of propionyl-CoA-genic amino acids (methionine and threonine) in Pcca-/-(A138T) mouse is much less compared to propionate accumulation. This could be due to the interrupted glucose and fatty acid metabolism which upregulates amino acids metabolism, even propionyl-CoA-genic amino acids metabolism might be inhibited by the accumulation of their downstream metabolite.

Limitation of study

Animal model of PA is a strong tool for pathological mechanism research. Mice are easy for gene manipulation. Much knowledge has been learned from mice experiment. However, the difference between mice and human needs to be taken into account. The relatively high residual PCC activity in muscles of Pcca-/-(A138T) mouse also complicates data interpretation.

References

Guenzel, A.J., Hofherr, S.E., Hillestad, M., Barry, M., Weaver, E., Venezia, S., Kraus, J.P., Matern, D. and Barry, M.A. (2013) Generation of a hypomorphic model of propionic acidemia amenable to gene therapy testing. Mol Ther 21, 1316-23.

He, W., Wang, Y., Xie, E.J., Barry, M.A. and Zhang, G.F. (2021) Metabolic perturbations mediated by propionyl-CoA accumulation in organs of mouse model of propionic acidemia. Mol Genet Metab 134, 257-266.

Wang, Y., Christopher, B.A., Wilson, K.A., Muoio, D., McGarrah, R.W., Brunengraber, H. and Zhang, G.F. (2018) Propionate-induced changes in cardiac metabolism, notably CoA trapping, are not altered by l-carnitine. Am J Physiol Endocrinol Metab 315, E622-E633.

17th Annual Tailgate Party for PAF

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, P.O. Box 151, Deerfield, IL 60015-4421. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us.*

ANNUAL REPORT 2021-2022

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.

2021-2022 Financials

Revenue:	
Contributions	$133,032
Interest	$87
Total Income	$133,119
Expenses:	
Program services	$103,857
Management & General	$2,444
Fundraising	$2,881
Total Expenses	$109,182
Cash Assets 8/01/2021	$431,754
Cash Assets 7/31/2022	$455,691

Board of Directors

Jill Chertow, President
Brittany Smith, Treasurer
Angela Waits, Secretary
Maria L. Cotrina

PROPIONIC ACIDEMIA FOUNDATION

Letter from the Board of Directors

We are happy to share with you our annual report.

This past year PAF has begun to go back to more "normal" pre-pandemic activities. We gave to small grant to the Community Health Clinic to host a PA Family Day activity for support in the Amish & Mennonite community. We also joined with HCU & OAA in hosting our first in-person conference since the onset of COVID-19.

PAF received our first education grant to work on developing new educational and support materials for families. The first two projects are expected to be completed in the fall of 2022.

We have been working with some new volunteers who are helping to expand PAF's reach and support to those who do not have English as a first language.

We thank you for your continued support for PAF as an organization and families touched by PA.

PROGRAM ACCOMPLISHMENTS

Grants Awarded

- Awarded $40,300 grant to Eva Richard & Eva Delpon, at Universidad Complutense de Madrid, Spain as a new grant for the project entitled: "Elucidation of cardiac electrophysiological alterations in propionic acidemia: Towards the identification of targets for therapeutics."
- Awarded $50,000 grant to Ken Maclean, PhD, at the University of Colorado Denver, USA as a continuation grant for the project entitled: "Chemical Chaperone Treatment to Restore Enzyme Activity in Folding Mutations of Propionyl-Co-A Carboxylase: Towards a Personalized Therapeutic Strategy in Propionic Acidemia (PA)."
- Awarded $842 grant to Community Health Clinic in Topeka, Indiana, USA to hold an education event in the Old Order Amish (OOA) community.

Support Activities

- In June 2022, PAF held a joint conference with HCU and OAA for "Land of the Free, Home of the Brave. Video recordings of the speakers are available for families to view online.
- Distributed fall and spring newsletters to affected families, clinicians, and donors
- Coordinated the Propionic Acidemia Foundation's Warrior Birthday Club in which students and staff at Oak Lawn Hometown Middle School and St. Linus School, Illinois, USA make birthday cards for those affected by PA, their siblings, and children.

Registry

114 Participants in the PA International Patient Registry. The Registry is an IRB-approved research project and the data collected will help characterize the condition of people living with PA.

Other Activities

- PAF received an educational grant from a pharmaceutical company for $8,500. The funds are being used to develop new educational & support materials for families affected by PA.
- Continued partnerships with other rare disease groups including: NUCDF, HCU, OAA, and NECPAD.
- Worked with pharmaceutical companies who are developing new treatments for PA and some who are currently holding clinical trials .
- Continued partnership with NHGRI Organic Acid Research Section who is performing a study entitled: Natural History, Physiology, Microbiome and Biochemistry Studies of Propionic Acidemia and developing a gene therapy for PA.
- Refreshed logo and Registry website.

Propionic Acidemia Foundation

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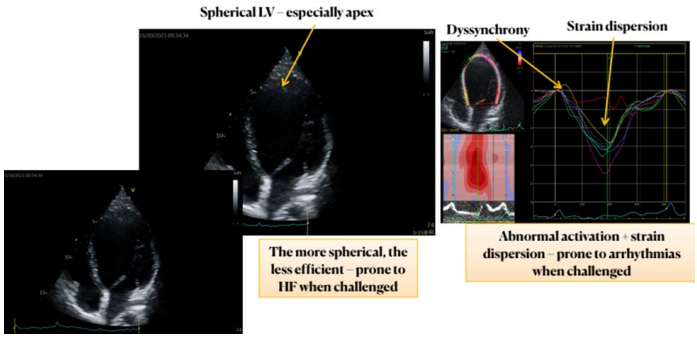
Cardiac Puzzle in Propionic Acidemia

Devyani Chowdhury, MD
Corey Snyder

Propionic Acidemia (PA) is an organic acid disorder caused by deficiency of propionyl CoA carboxylase leading to impaired supply of succinyl CoA to the Krebs cycle. The Krebs cycle is a metabolic function where the body generates energy after the breakdown of nutrients. PA presents with a wide spectrum of symptoms and age of onset, from mild to life-threatening phenotype with manifestation of cardiomyopathy. In the Amish community the condition is often detected via the newborn screen. PA patients may develop cardiomyopathy and some have reported sudden death. The exact cause and mechanism of sudden death is unclear.

It is important to take a deep dive into the cardiac phenotype by performing assessment of heart function and rhythm. EKGs, echocardiogram (ECHO), Holter monitors, and extended rhythm monitoring are often helpful. The EKG and holter monitor collect heart rhythm information, while the ECHO determines structure and function of the heart. It is important to get an assessment of the heart at the time of diagnosis of PA.

As seen on the ECHO image, PA typically causes the shape of the heart (left ventricle) to become more rounded or spherical, especially around the apex. The abnormal rounded shape implies an outside stress causing the heart to work harder than usual. A more rounded left ventricle causes the heart to be less efficient and prone



to heart failure when challenged. There also may be electrical and rhythm issues in the heart. Changes in shape and function may lead to a higher incidence of arrhythmias that can be exacerbated by stress on the heart.

Certain medications can significantly decrease afterload of the heart, to increase ventricular stroke volume and decrease the work of the heart. Lifestyle changes may also help preserve the cardiac function and decrease the stress on the heart. It is important to work with the cardiologist to manage medications and lifestyle changes. The cardiac changes are still not well understood. More research is required in this area. It is however important to have an assessment of the heart in PA patients. *For more information on a cardiac evaluation please contact Dr. Chowdhury's office, Cardiology Care for Children, Lancaster PA at 717-925-8300.*

PAF Funded Research Update

ABERRANT PROTEIN PROPIONYLATION AND DISTINCT HISTONE MARKS IN PROPIONIC ACIDEMIA: NEW DISEASE MECHANISMS AND RISK FACTORS FOR CARDIAC DISEASE

PI: Pawel Swietach (Oxford University)

Patients affected by propionic acidemia (PA) present with disturbances in the levels of metabolites, notably propionate. This small (three-carbon) molecule is normally produced from the breakdown of substances in the diet, such as branched-chain amino acids and odd-numbered fatty acids. In PA, however, genes responsible for propionate processing are inactivated by inherited mutations. A long-standing view postulates that the ensuing biochemical milieu is responsible for the dysfunction of multiple organs affected in PA.

Understanding how the heart is affected in PA is particularly important, because many childhood deaths have been linked to cardiac disease. However, the precise mechanism linking the metabolic disturbance with heart disease in PA is unclear. Without this detailed information, it is difficult to propose new cures and improve disease management before viable gene therapies are available. Moreover, knowledge of the molecular mechanisms has broader impact on cardiac health, because elevations of propionate have also been described in other diseases, such as diabetes.

The aim of our PAF project was to investigate how the metabolic derangements in PA affect proteins through so-called post-translational modifications, i.e. chemical 'editing' that can affect their functions.

Using a mouse model of PA, we showed that histones, the protein scaffold of DNA, undergo two types of modifications in the heart: propionylation and acetylation. We then demonstrated how these actions affect the expression of genes in the heart. Strikingly, we found that several genes, previously implicated in cardiac disease, become aberrantly activated in PA, and we speculate that dampening this PA-driven genetic response may alleviate the pathological changes experienced by patients. Through our observations of the mouse model of PA, we identified a novel biochemical pathway that offers an alternative means of processing excess propionate in the heart. Activation of this pathway was associated with a less severe disease presentation in mice. We hypothesize that this pathway could be exploited therapeutically in PA patients, and our immediate aims for the future are to identify the best approach for exploiting this protective reservoir for propionate in the heart.

In summary, the PAF project has (i) delivered novel mechanistic insights into how propionate affects the heart using state-of-the-art methods in metabolomics, transcriptomics, chromatin biology, and physiology, and (ii) revealed new pathways for propionate processing that by-pass the mutated enzymes in PA patients.

Red cataract in propionic acidaemia

B Staniszewski[1], S Patel[1], S Burgess[2]
1. Department of Ophthalmology, Ninewells Hospital and Medical School, Dundee
2. Department of Ophthalmology, NHS Forth Valley, Falkirk Community Hospital, Falkirk

Systemic and Ophthalmic Manifestations of Propionic Acidaemia

Propionic acidaemia is a rare autosomal recessive disorder (incidence, less than 1 in 100,000) that causes chronic metabolic decompensation with paroxysmal ketoacidosis, failure to thrive and developmental delay. The condition is caused by deficiency in propionyl-CoA carboxylase which plays a role in the normal breakdown of proteins, fat and cholesterol. As a result, a substance called propionyl-CoA and other potentially harmful compounds accumulate in mitochondria, causing bone marrow suppression and metabolic acidosis.

With timely clinical intervention and improved management, patient survival time has lengthened considerably in recent years.

Several studies have previously demonstrated an association between propionic acidaemia and optic nerve atrophy [1,2]. There have been no reports of lens opacities in patients with propionic acidaemia described in literature.

Aim

To report an unusual case of red cataracts in association with propionic acidaemia and discuss its management.

Case Presentation

26 year old male with a diagnosis of propionic acidemia first presented to the eye clinic for visual assessment at the age of 10. His visual acuities (VA) were 6/9.5(OD) and 6/38(OS). Fundal examination showed mild temporal pallor of the left optic nerve head. He subsequently developed progressive optic nerve atrophy in both eyes. Due to patient's learning difficulties, VA assessment has been challenging and variable VA have been documented during his clinic visits. The patient has received multiple sessions of hyperbaric oxygen therapy with reported improvement to wellbeing and quality of vision by patient's mother. The patient has gradually developed bilateral, symmetrical lenticular opacities of unusual morphology. Both lenses had a distinct red/amber discolouration. Following a discussion of risks and benefits, we have proceeded with left cataract surgery.

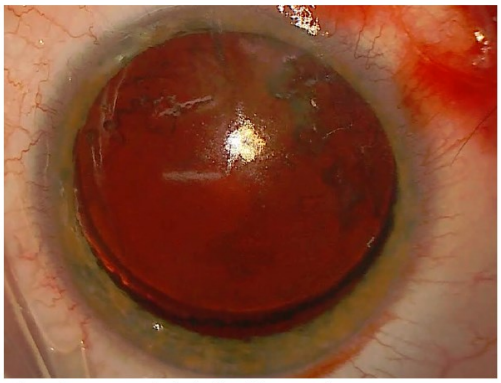


Fig1. Left cataract at the beginning of the operation

Cataract Surgery

Left phacoemulsification and IOL insertion was performed under sub-Tenon's local anaesthesia. The surgery resembled a paediatric cataract extraction. The anterior capsule was elastic. Vision blue and high viscosity cohesive viscoelastic (Microvisc plus) were used. The crystalline lens was soft and removed with aspiration only.

There were no intraoperative complications and VA(OS) documented preoperatively as 60 ETDRS letters at 2m improved to 0.05 Sonksen LogMAR visual acuity at 1 week postoperatively.

More importantly, both the patient and his mother have reported a significant improvement to patient's quality of vision and visual alertness.

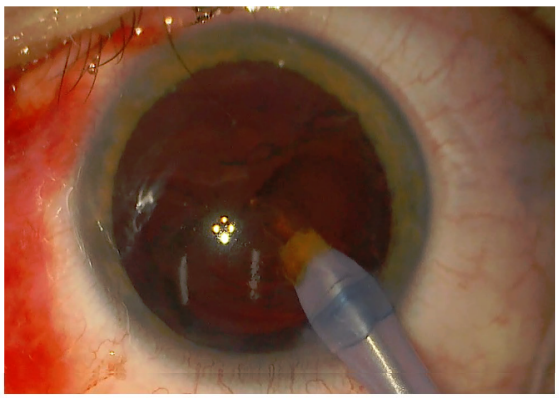


Fig 2. Aspiration of lens material

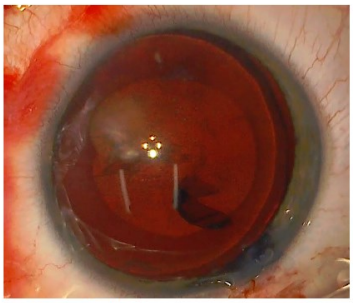


Fig 3. Capsulorrhexis

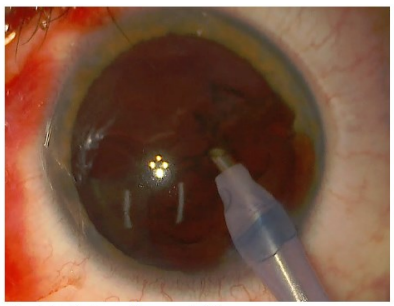


Fig 4. Aspiration of lens material

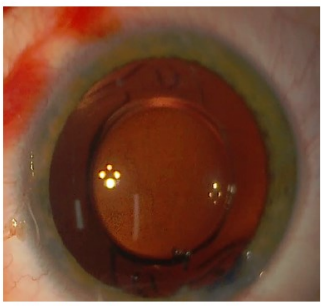


Fig 5. Posterior chamber lens implant

References:
1. Ianchulev T, Kolin T, Moseley K, Sadun A. Optic nerve atrophy in propionic acidemia. Ophthalmology. 2003 Sep;110(9):1850-4.
2. Martinez Alvarez L, Jameson E, et al. Optic neuropathy in methylmalonic acidemia and propionic acidemia. Br J Ophthalmol. 2016 Jan;100(1):98-104.

PAF EVENT & FUNDRAISING SPOTLIGHT

UPCOMING EVENTS

- **November 6, 2022 - Team PARunners New York Marathon**
- **March, 4, 2023 - PA Family Conference, Chicago, IL**
- **July 22, 2023 - PA Education Day, Ohio - Save the date!**

PAST EVENTS

- **PA Chats**
- **17th Annual Tailgate Party & Corn Hole Tourney for PAF, estimated $10,000!** (photos on pg. 5)

GIFT MATCHING: This may enable you to double your donation. Check with Human Resources to see if your employer matches. It makes a big difference.

FACEBOOK: Thank you to all of our Facebook Fundraisers and people that donated to their fundraising pages for birthdays, #GivingTuesday or just because: Linda Chell, Lisa Shutts-Mash, Amy Wilson, Abbie Marie, Erika Gross, Cindy Olhoft, Susan Marks, Nancy Hudson, Kim Mangold

STOCK DONATIONS: PAF is now accepting stock donations. Please email paf@pafoundation.com with any questions.

DEDICATED GIFTS FROM INDIVIDUALS:
Among the many contributions received, the following is a list of some that were dedicated to those who have inspired the giver.

- **In Honor Of**: Trent McKinley, Kate Lowry, Gennan and Cody Lenert
- **In Memory Of**: Talli Smith, Blake Chell, David Scott, Jordan Franks

STOCK DONATIONS: PAF is now accepting stock donations. Please email paf@pafoundation.com with any questions.

Matching Donations and Volunteer Hours: Some companies have a volunteer program and will donate based on your volunteer hours. PAF is always looking for volunteers. Please check with Human Resources to see if they have a program. In addition, some companies will match your donation.

INTERNET

Thank you for using Igive, Goodsearch and AmazonSmile and designating Propionic Acidemia Foundation as your charity and setting up Facebook Fundraising Pages. Every dollar counts.

Thank you for all donations and the kind notes we receive throughout the year. Your support overwhelms us and continues to be a source of inspiration. PAF couldn't do what we do without your incredible support.
Thank you for making a difference.

COMMUNITY HEALTH CLINIC PROPIONIC ACIDEMIA FAMILY DAY

Through the generosity of the Propionic Acidemia Foundation (PAF), The Community Health Clinic (CHC) held a Propionic Acidemia Family Day on May 21st 2022. Historically, the Old Order Amish (OOA) community has been a medically underserved community due to several barriers to care including transportation, cultural, financial, and others. Unfortunately, the OOA community has a disproportionate number of genetic diseases due to the founder effect (community members descending from a few founding families), endogamy (preference to marry only within the community who has shared genetic background), and large family sizes. Some Indiana OOA community members have propionic acidemia (PA) due to the pathogenic variant c.1606A>G in the PCCB gene. Unfortunately, this variant has been missed on NBS. Though this variant may not be considered the severe type of PA, left untreated, it can manifest with serious and even life-threatening complications. In addition to diagnosis and treating community members with PA, the CHC aims to educate the local community about PA in order to lead to more rapid diagnosis, accurate treatment, participation in research, and ultimately lead to better health and quality of life outcomes for those in the community with PA.

Methods:
This family day was previously planned for April 2020, but due to the COVID-19 pandemic, the family day was postponed. As part of previous PAF funding, the CHC conducted a PA testing program in the community despite having to postpone the family day. The rescheduled family day was held on May 21st 2022, which was attended by known PA families from our clinic. Letters were mailed to all known families prior to the event. In total, 15 invitations were sent.

Results:
The CHC PA Family Day was attended by four families during the morning breakfast session. This session was intended for families to have time for fellowship. Of the four families in attendance, two families were from Michigan, and two families were from Indiana. Six affected children were in attendance during this session, ages 3 months old to 14 years old. During the afternoon education/lunch session, attendees had presentations from cardiologist Dr.

Chowdhury, geneticist Dr. Zineb Ammous, and Jill Chertow from the PAF. Overall, 23 Amish community members were in attendance. Attendees learned more in depth about the cardiac involvement of PA, the genetic cause of PA, clinical information about the Amish variants, guidelines for treatment, and PAF. Given that PA families were gathering for the event, the CHC took the opportunity to offer genetic testing for co-morbid types of cardiomyopathy and was able to test three patients with PA at the event.

This testing has become part of the CHC's PA care as OOA patients with PA could have other genetic forms of cardiomyopathy. Additionally, two patients with PA saw the visiting cardiologist for cardiac evaluations in the days prior to the event. While the cardiac testing and evaluation were not part of this funded program, they were targeted to occur at or in close proximity to the event for family convenience to increase uptake of health services for patients with PA.

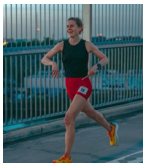
OFFICIAL CHARITY PARTNER

NOVEMBER 06, 2022
TCS NEW YORK CITY MARATHON

Meet our amazing 2022 NYC Marathon PA runners. For more about their stories, check their fundraising pages.

Cody Hicks, New York, USA. "This will be my 10th marathon milestone. I'm raising money to help fund research to find a cure for Propionic Acidemia. My friend and team leader Marisa's son Gabriel has this rare serious genetic disorder. Please support my fundraising efforts for the 2022 TCS New York City Marathon Fundraising." https://fundraisers.hakuapp.com/fundraisers/ca12ec11df6aa6a6a3ab

Caroline J Biega, Vancouver, CANADA. "I met Aubrey Delima and her husband in May 2019. I learned that they had two daughters born with this disorder. I am aware of the challenges and obstacles necessary to overcome and successfully complete the 42.2 Km/26.2 miles. These challenges are nothing in comparison to the challenges and obstacles families with members affected by PA deal with -to-day for life." https://fundraisers.hakuapp.com/fundraisers/cf2f063c009dbec45ed7



Evelyn Baert, New York, USA. "I am running this race for my mother's nephew, Juanito, who lives in Ecuador and has PA. His father, Sebastian, asked me if I would run on their behalf and I could not be more honored to run this race for them and for all the families who are battling PA." https://fundraisers.hakuapp.com/fundraisers/d91e4015ec4d9c48d467

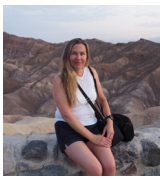
Aubrey Delima, Vancouver, CANADA. "Our daughters, Jenna and Lauren were born with Propionic Acidemia. Lauren passed away at the age of 9 (in 2010) due to complications of this disease. By the grace of God, Jenna is stable and is now 23 years old! I will run the New York City Marathon on Nov. 6, 2022, with a small group fundraising for the Propionic Acidemia Foundation (PAF). " https://www.gofundme.com/f/aubrey-runs-ny-marathon-for-paf

Deborah Slipetz, New York, USA. "This year I will be running the 51st Edition of the New York City Marathon, raising funds in support of the Propionic Acidemia Foundation (PAF). Running for PAF is really close to my heart, as this disease affects Gabriel, son of my colleague Juan Carlos Lopez and his wife, Marisa Cotrina. We're closer than ever to a cure for PA, and your generous support will make it possible." https://fundraisers.hakuapp.com/fundraisers/beffb108c940a5eab39e

John Moss, St Louis-Missouri, USA. "When our twins Grant and Sebastian were born with PA, we were fortunate to be in a hospital with a university geneticist and insurance coverage. But as they started to crash, even their doctors had very little information about what they had, just a lot of scrambling to try and save them. So, I feel raising money for PAF is helping every parent that has a child with PA." https://www.gofundme.com/f/john-moss-tcs-2022-marathon

Joseph Suarez, Vancouver, CANADA. "My nieces, Jenna and Lauren, were diagnosed with PA. My family and I have witnessed the devastating and bold truths that accompany this disease." https://gofund.me/af2c2dc5

Wesley Scott, Vancouver, CANADA. "I will be running in the New York Marathon on Nov 6, 2022 with my good friend Aubrey. Please help us achieve our goal." https://www.gofundme.com/f/raising-awareness-for-propionic-acidemia



Kelly Goldman, Vancouver, CANADA. "I am honored to be running the NYC marathon in support of PAF. I have been struggling with motivation returning to running after my own illness, so when the opportunity arose to join the charity runners, I grabbed it. What better way to support a worthy organization AND to get myself moving (slowly!) again."

Owen Staiger, New York, USA. "Your contribution means a lot to me as a runner but also to the Propionic Acidemia families and everyone in the Propionic Acidemia community!"

https://fundraisers.hakuapp.com/fundraisers/34aee9d9c8781ac3d160

Searching for a Cure
Hope for Our Children

Propionic Acidemia Foundation
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Deerfield, IL. 60015

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