Potential Biomarker Discovery for Dilated Cardiomyopathy in Patients with Propionic Acidemia Using a Targeted Approach from Cardiovascular Literature

THE COLLEGE OF WOOSTER

Nicholas R. Bositc
Advisor: Dr. Paul E. Edmiston
2nd Reader: Dr. James D. West

Department of Biochemistry and Molecular Biology,
The College of Wooster
Wooster, OH 44691

Objective: Find statistically significant potential biomarker(s) for dilated cardiomyopathy in Amish patients with propionic acidemia.

Background

Amish patients with **propionic acidemia (PA)** are homozygous for a missense variant in the PCCB gene (c.1606A>G; p.Asn536Asp), encoding for the beta subunit of propionyl-CoA carboxylase (Fig. 1). Causing a high ratio of propionyl-CoA to acetyl-CoA (the reverse of healthy patients). Along with a large buildup of other downstream metabolites (Fig. 2). Ultimately patients with PA develop **dilated cardiomyopathy (DCM)**, characterized by a dilated heart with a decreased ejection fraction (Fig. 3). DCM will eventually lead to heart failure if not carefully treated, usually presenting at a young age. Creating a need for newborn screening in PA patients and careful monitoring.

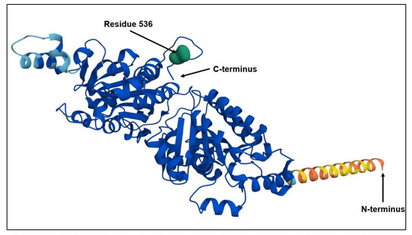


Figure 1. Propionyl-CoA carboxylase beta chain subunit.

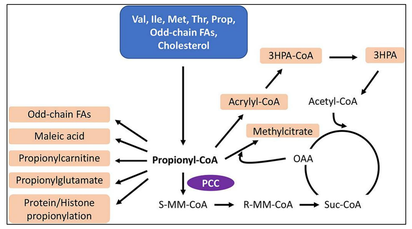


Figure 2. Propionyl-CoA Carboxylase Pathway. *Marchukq, H., Wang, Y., Ladd, Z. A., Chen, X., and Zhang, G.-F. (2023) Pathophysiological mechanisms of complications associated with propionic acidemia. Pharmacol Ther.* ***249****, 108501*

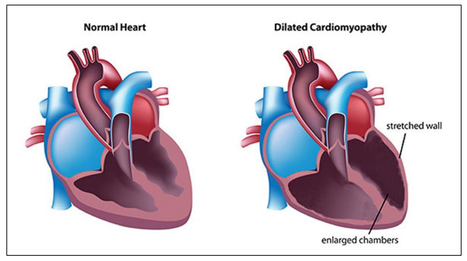
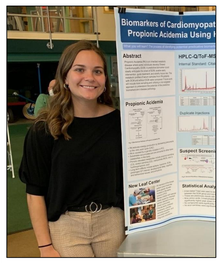


Figure 3. Dilated Cardiomyopathy presenting in the heart.

Figure 4. New Leaf Center in Mount Eaton Ohio.



Alexa Bencic

Dr. Olivia Wenger

In 2021 **Alexa Bencic** partnered with **Dr. Olivia Wenger**, who started the **New Leaf Center** to treat rare diseases in the adolescent and adult Amish Community. There was a need to research this relationship between DCM in Amish patients and PA.

Over a 3-year period 86 serum samples from 21 young Amish patients were provided and tested for this relationship using different metabolomic techniques by Bella Coenen and Riley McErlean. Although some results were found, there was still a wide area of metabolomics that needed to be explored for this relationship.

NEW LEAF CENTER
CLINIC FOR SPECIAL CHILDREN

Methods

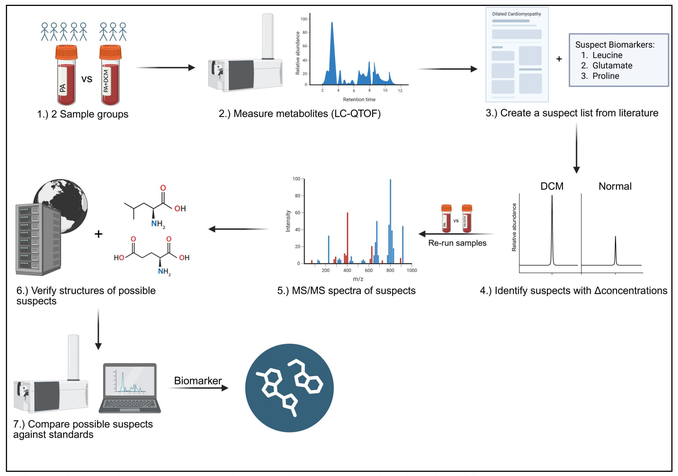


Figure 5. Overview of the targeted metabolomic approach using the CSL.

The goal of this project was a hypothesized driven approach to pursue finding a potential biomarker for DCM in PA patients. The novel part of this process was the creation of a Cardio-literature Suspect List (CSL), built using metabolomic conducting clinical literature of other heart diseases and/or conditions. To create the CSL clinical literature relevant to heart diseases and/or heart conditions was searched against certain criteria.

Table 1. **Criteria for inclusion on CSL.**

Essential Criteria
1a. Metabolite is related to untargeted cardiovascular research and/or related heart function literature
1b. Metabolite is a known human metabolite
2. Metabolite is mentioned in 2 or more papers
Non-essential Criteria
3. Has 2-fold change vs control samples in papers
4. Can be tested against commercial standard
5. Can be recognized in positive ion mode (vs. Negative ion mode)

Once the suspect list was created, each suspect metabolite was screened for statistically significant differences between the two groups (PA cohort vs PA+DCM cohort). After, structural identities of suspect features with statically significant Δabundance differences were confirmed using MS/MS spectra (Fig. 6)

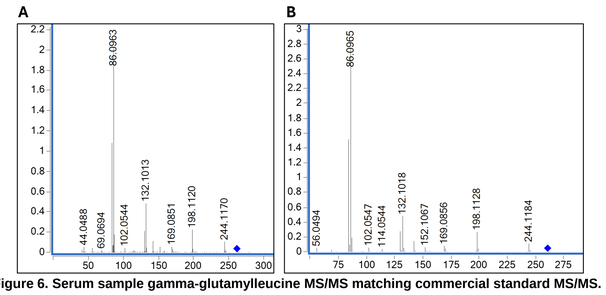
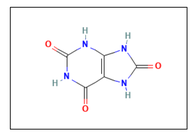


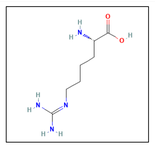
Figure 6. Serum sample gamma-glutamylleucine MS/MS matching commercial standard MS/MS.

Results

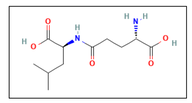
Mass Compound Name	DCM vs No DCM	+ or - Literature	P	Δppm Average	Retention Time	Schmanski Score
168.0289 Urate	+	+	$5x10^{-5}$	2.75	4.1	1
188.1273 Homoarginine	+	-	$1x10^{-4}$	-0.74	2.5	1
260.1369 Gamma-glutamylleucine	+	+	0.014	-2.45	14.6	1
309.1058 N-acetyl-neuraminic acid	+	+	0.033	-0.33	2.7	1
289.1528 3-Methylglutaroylcarnitine	+	+	$9x10^{-4}$	0.90	10.9	2a
169.0849 3-methylhistidine	+	+	0.001	-0.46	2.5	2a
297.1072 Methylguanosine	+	+	0.008	-0.66	10.8	2a
118.0263 Succinate	-	+	0.003	-3.70	2.5	2a
246.1218 Gamma-glutamylvaline	+	+	0.007	0.90	10.7	2a



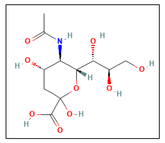
Urate



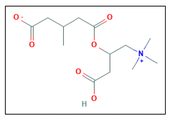
Homoarginine



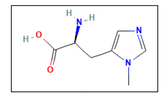
Gamma-glutamylleucine



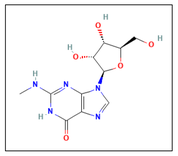
N-acetyl-neuraminic acid



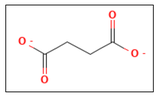
3-methylglutaroylcarnitine



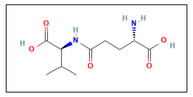
3-methylhistidine



methylguanosine



succinate



gamma-glutamylvaline

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