Transcriptional regulation of fatty acid beta-oxidation in public cardiomyopathy datasets

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Abstract

A lot of research intro the metabolism changes during cardiomyopathy has been done. It is known that the rate fatty-acid beta oxidation (FAO) is changed in diseased hearts. Dependingn i on the origin of the cardiomyopathy and the type, FAO is either regulated up or down. How this is regulated transcription wise is not yet fully understood. In this review we show that a lot of research into this regulation is messy and can state contradicting results. But it is also shown that some interesting patterns can emerge from the combined results. Showing the importance of public data sets and making a case for a widespread database combing all current datasets.

Introduction

Cardiomyopathy is the central name for a group of diseases affecting the pumping ability of the heart muscle. The common denominators within this group are alterations in ventricular wall diameter, chamber size, or contractile function[1]. There are many types of cardiomyopathies, each showing a different pattern in alterations of the heart structure. Ischemic cardiomyopathy (ICM) is a form characterized by narrowed or fully occluded coronary arteries, resulting in cell death[2,3]. Hypertrophic cardiomyopathy (HCM) is characterized by an unusually thickened heart muscle[4]. In restrictive cardiomyopathy, the lower walls of the heart chamber become too rigid, which results in the heart not being able to expand to its fullest when filling with blood[5].

The most common type is dilated cardiomyopathy (DCM), in which the whole heart is expanded. Each type of cardiomyopathy results in the heart not being able to pump blood around the body as effectively as in a healthy person[1,2,4,5]. The cause of these abnormalities is in some cases inherited. In an example, a study into the relatives of cardiomyopathy patients showed that a large amount had a single gene mutation in structural proteins of the myocyte cytoskeleton or sacrloemma[6]. Another example is a X-linked form of cardiomyopathy, which is seen in males in their teen years. This type of inherited cardiomyopathy is characterized by elevated serum creatine kinase muscle isoforms[7]. While on the other hand cardiomyopathy can be caused by non-genetic causes, for example diet. Patients with diabetes, which can be caused by a bad diet, are shown to have a higher chance of developing

cardiomyopathy[8]. Stress is also shown to increase the chances of developing cardiomyopathy[9].

The human heart uses a lot of energy, while it is contracting around the clock[10]. Failing hearts show a large decline in ATP concentrations, showing up to 30% less ATP present in the heart tissue of cardiomyopathy patients[11,12]. In healthy hearts this ATP is harvested for the most part from the oxidation of fatty acids, being almost 70% of the produced ATP. The other part is harvested from the oxidation of carbohydrates, such as glucose. Because fatty-acids used in FAO are not stored in the human heart, results in the uptake of these lipids being highly controlled. It has been shown that in patients suffering from heart failure, this balance in FAO and carbohydrate oxidation is skewed[13]. The suffering heart is suddenly changing its energy sources. In failing hearts the utilization of FAO to produce energy is strongly reduced, while the oxidation of glucose is increased. This increase in glucose oxidation can lead to cardiac glucotoxicity. In patients suffering from heart failure caused by obesity or diabetes show an increase in FAO, while harvesting less energy from glucose[14]. In both cases, the change in FAO has huge consequences. although the up- and down-regulation of this FAO are not fully understood yet, it appears that it is mainly the result of an alteration in genes that are regulated by the PPAR-trio, PPAR-alpha (*PPAR-α)*, -beta/delta (*PPARD),* and -gamma (*PPARG*)[15,16]. These three transcription factors appear to regulate a whole set of genes of which many are involved in the regulation of FAO. To get a better understanding of which deferentially expressed genes (DEGs), associated with the regulation of FAO are commonly seen up-or down-regulated in cardiomyopathy patients. This research will not only focus on papers directly investigating the regulation of FAO in cardiac tissue but will also look into broader transcriptome experiments performed on diseased cardiac tissue. All this is done to get a better insight into the *Transcriptional regulation of fatty acid beta-oxidation in public cardiomyopathy datasets.* In total 19 different datasets were found that performed an RNA-seq experiment to look and the DEGs between heart patients and healthy persons. I hypothesize that there is a different expression pattern between different types of cardiomyopathy.

Results

To get insights into the transcriptional regulation of fatty acid beta-oxidation in public cardiomyopathy datasets, the search scope had to be altered multiple times. This was done because throughout the process it was discovered that a lot of research was done with either unreliable methods and on model organisms or that most research does not specifically target

the regulation of FAO in cardiomyopathy but has a broader scope. This is why the project was performed in three phases.

1) *General insight in lipid metabolism regulation in diseased heart tissue*

2) *RNA-seq experiments on lipid metabolism regulation in human tissue*

3) *Setting up a gene list and comparing this to general RNA-seq experiment in diseased human heart tissue*

Each phase resulted in findings that did not end up in the final results but provided a deeper insight into the total landscape of FAO regulation research in human tissue. They, however, also showed where there still is a lack of information.

Phase 1. general insight in lipid metabolism regulation in diseased heart tissue

At the start of the research, all papers were selected that researched FAO in cardiomyopathy. This resulted in a large number of papers, published as early as 2001 and as recent as 2019(supplementary table 1)[17,18]. Numerous papers focused on a small subset of genes but some papers researched the whole transcriptome[19–22]. But two aspects of these papers made many not quite fitting for the goal of the research. Firstly, a large number of papers performed their whole research only on model organisms, such as mice, dogs, mini pigs, and other animals[23–25]. Although the use of model organisms has been used for ages and has often been translated into human tissue, this can't be guaranteed. A lot of research needs to be conducted to confirm that the findings in a model organism are the same in humans. Mainly because that the metabolism, especially the cardiac metabolism, can significantly differ from that of humans [26,27]. Secondly, a significant part of the papers found performed microarray experiments. Microarray experiments, in which DNA spots are attached to a glass surface to measure expression levels, are based on advance produced probes. These probes show a large bias in hybridization strength to probes with a comparable sequence. Which could result in misleading information. Besides this bias, because the probes are made in advance, they are often based on known gene models. Which makes them less suited for identifying novel genes[28–30]. A new technique was developed that did not have this bias and was great at discovering novel genes, namely RNA-sequencing (RNA-seq)[31].

Phase 2. RNA-seq experiments on lipid metabolism regulation in human tissue

After concluding that the first scope was too broad, it was narrowed. Here selection took place on papers only researching FAO in human samples, only via RNA-seq experiments (Supplementary Table 1). The goal was to focus purely on the transcriptional regulation of fatty acid beta-oxidation in public cardiomyopathy datasets. This led to only a hand full of papers, of which only one was found in the previous phase[18]. This group of papers started to show some overlap in gene regulation, showing a small subset of genes that were found in a large number of papers[32,33]. One of which was *PPAR-α*, which as already stated is suggested as a key regulator in the FAO regulation[34]. although there are plenty of papers performing RNA-seq experiments on human cardiomyopathy patients, not many focused solely on FAO. This shows the differences between microarray and RNA-seq experiments, while microarray experiments were often focused and narrowed down, RNA-seq experiments scale a broader terrain. This resulted in one last change of scope, into a broader search field combined with a narrowed gene set.

Phase 3. Setting up a gene list and comparing this to general RNA-seq experiment in diseased human heart tissue

After discovering that many RNA-seq gene expression experiments performed on cardiomyopathy researched a broader spectrum than some as FAO regulation a new approach was set up. The idea was to combine as many RNA-seq experiments on cardiomyopathy patients as possible and look for interesting DEGs. Firstly a set of genes was selected via the gene ontology project. This resulted in a set of 76 genes (supplementary table 2)[35]. Besides this list, the gene *KLF15* was added. *KLF15* is a transcription factor associated with regulation of the cardiac metabolism[36]. And it has been suggested that *KLF15* closely cooperates with *PPAR-α* and seems essential in the *PPAR-α* mediated gene expression[37,38]. Resulting in a total of 78 genes associated with FAO and investigated in this paper.

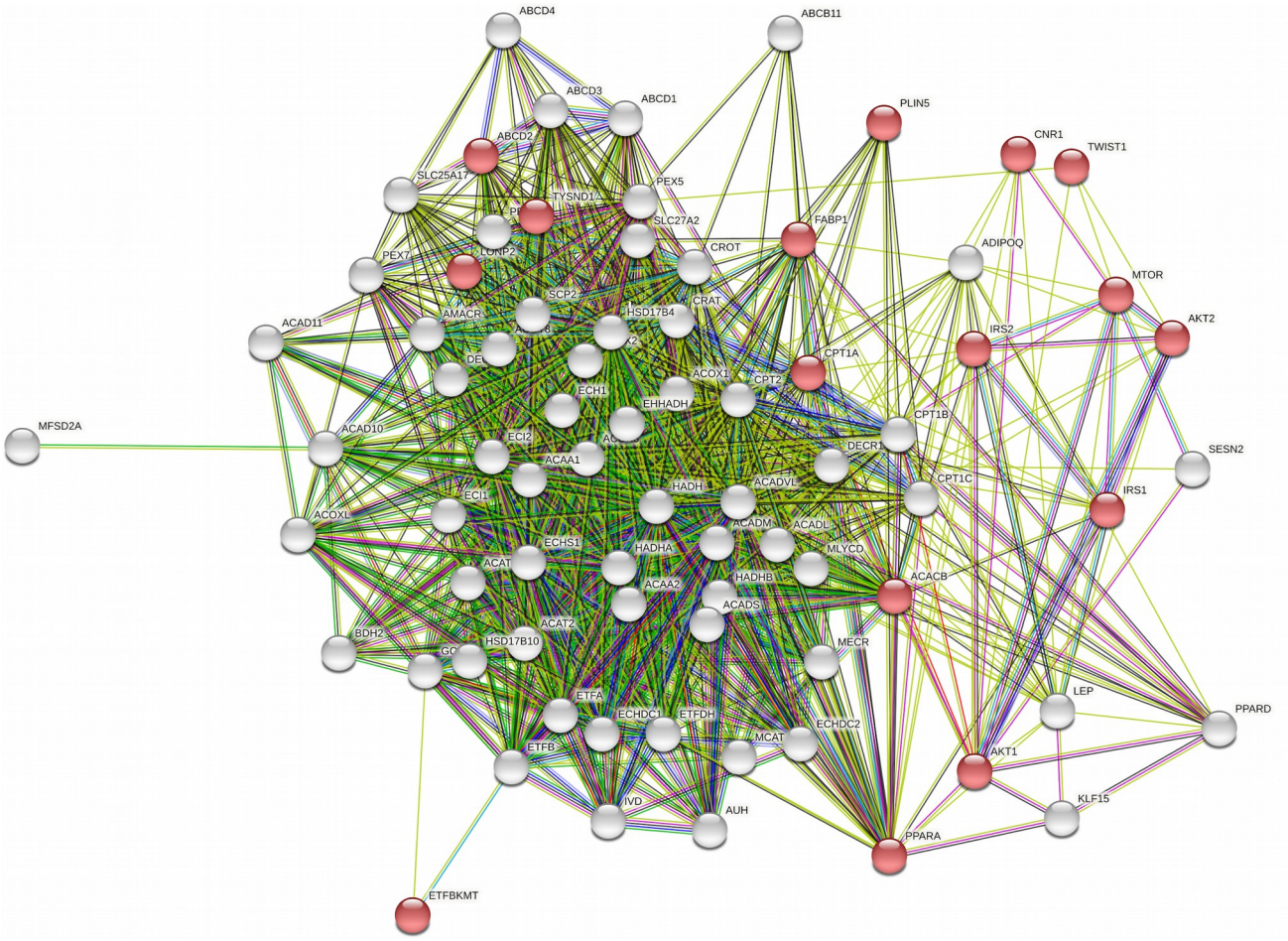


Figure 1. protein-protein interactions. *The results of a protein-protein interaction analysis of all 78 genes associated with FAO. Dots in red are genes associated with the regulation of FAO (GO:0031998). Edge colors show interaction evidence type. cyan/Lila: Known interactions, green/red/blue: predicted interactions, light green: text mining, black: co-expression, light purple: protein homology.*

In a protein-protein interaction analysis it is shown that all proteins encoded by the genes associated with FAO and thus selected for investigation, do interact with each other (supplementary figure 2, figure 1). From the 78 genes associated with FAO, 16 genes were directly associated with the regulation of FAO via gene ontology(figure 1, GO:0031998). After this gene list was set up the goal was to find papers investigating DEGs in cardiomyopathy patients and search for any of these 78 genes to look for expression patterns that might suggest regulation of FAO (Figure 2).

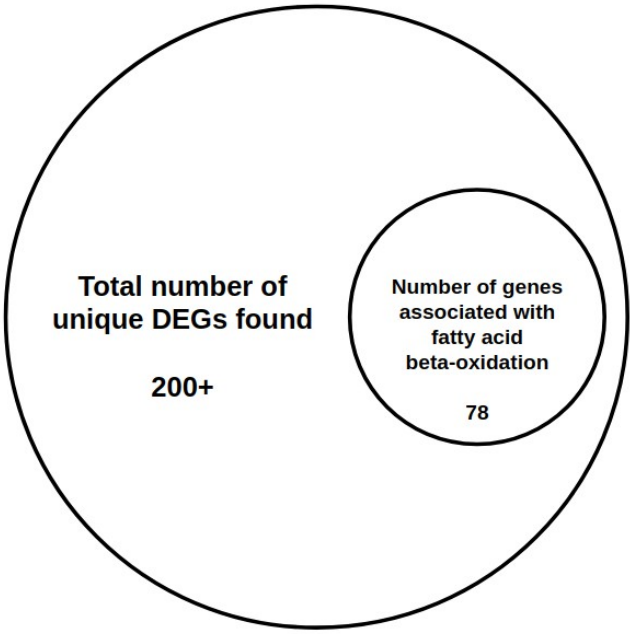


Figure 2. Summary of research. *Venn diagram showing the small subset of genes found in a large set of DEGs found in 15+ papers*

Paper overview

In total 19 relevant papers were found(supplementary table 3, figure 3)[18,20,21,25,32,33,39–51]. Paper publishing dates spanned from 2015 to 2020. All except one paper mainly focused their research on humans with one paper focussing on dogs and validating their results in human cells. All experiments mainly performed an RNA-seq experiment, a single paper performed a microarray experiment but was still added. This paper was added because it focused specifically on FAO and showed enough relevance to still be added. In total, all 77 genes were found either up- or down-regulated in at least one paper. Some papers did not submit their DEGs online but were still added because of the nature of the paper and its relevance (n/a: figure 3). In total five papers did not submit their data online and three only supplied their data upon request (n/a: raw-data, processed data. Figure 3) concerning privacy considerations. All papers except one used RNA extracted from human heart tissue while four papers cultured cardiomyocytes. In total four different types of cardiomyopathy were investigated, with both ischemic cardiomyopathy and dilated cardiomyopathy being the most investigated types (figure 3.)

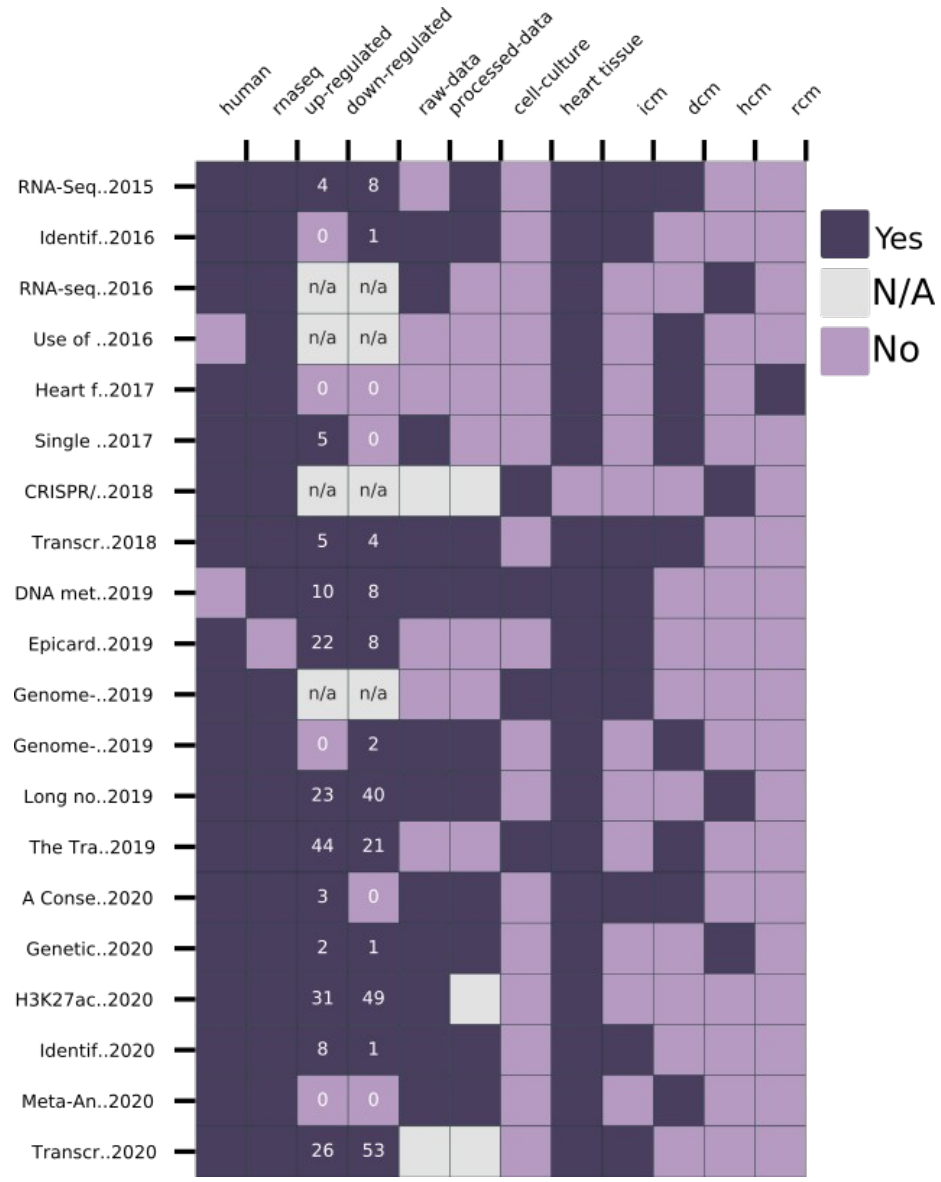
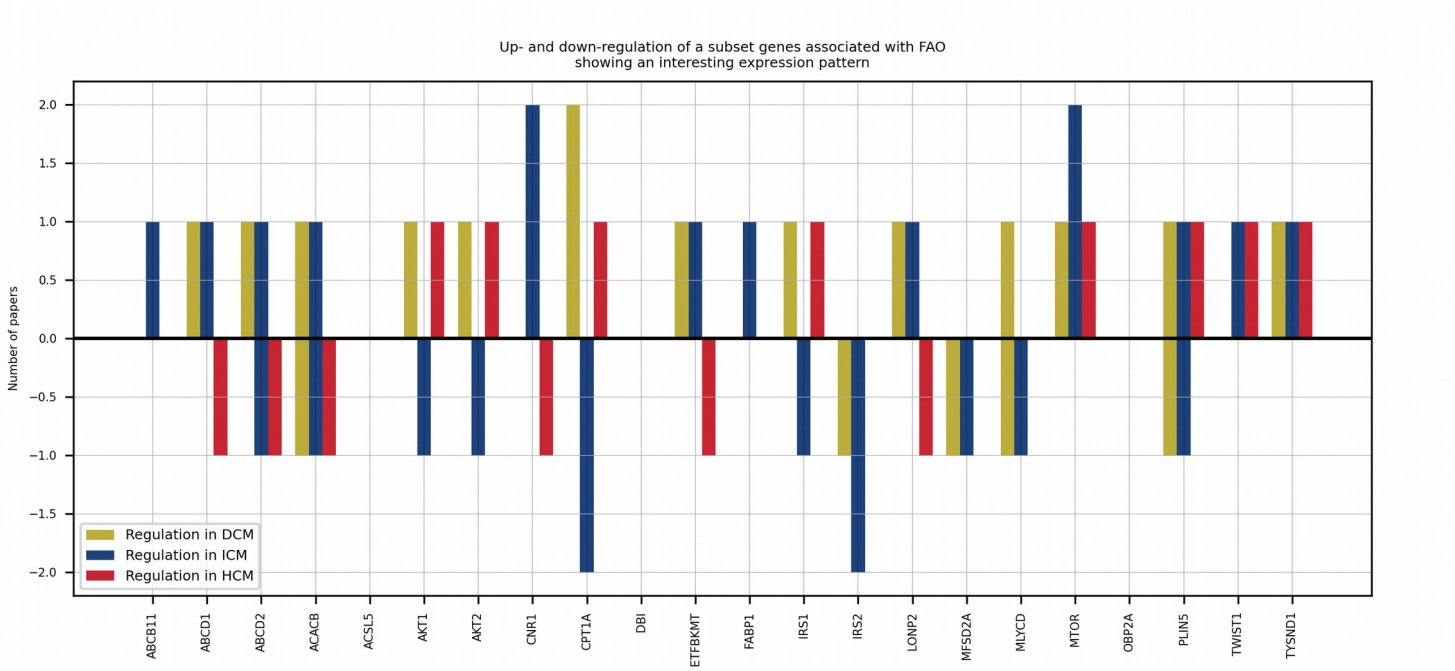


Figure 3. Summary of all papers found. *All relevant datasets are found in different papers (y-axis) and summarising information about the papers. Meaning of n/a in up- and down- regulated; the DEGs were not uploaded by the authors, raw- and processed-data; the data is only available on request. ICM: ischemic heart disease, DCM: dilated cardiomyopathy, HCM: Hypertrophic cardiomyopathy, and RCM: Restrictive cardiomyopathy.*

Differentially expressed gene patterns

In total, all 77 genes were wound to be differentially expressed in at least one paper (supplementary figure 1). The results were split over the different types of cardiomyopathy that were found in the papers. Restrictive cardiomyopathy was left out here because only a single paper analyzed this type of cardiomyopathy and it did not show any of the 77 genes to be either significantly up- or down-regulated. Some genes show a clear expression pattern. *ACAT1* and *ACAT2* are two genes that are down-regulated in all three different types of cardiomyopathy (figure 4, supplementary figure 1). acetyl-coenzyme A acetyltransferases

(*ACAT*) are membrane proteins in the endoplasmic reticulum that help with the transformation of fatty-acids into cholesterol[52]. *ACAT1* and *ACAT2* are two isoforms that both acts in this pathway and are linked to cholesterol homeostasis (figure 4, supplementary figure 1). Inhibition of either of these genes proved problematic and led to cholesterol accumulation[53]. On the other hand, *ACAD10* and *ACAD11* show clear up-regulation in ischemic cardiomyopathy. Both of these genes are family of acyl-CoA dehydrogenases (*ACADs*), which participate in the cycle of b-oxidation to produce acetyl-CoA[54]. Thus upregulation of these genes seems to be linked to more FAO. *CPT1A* also shows a promising pattern, with this gene being unregulated in both dilated- and hypertrophic-cardiomyopathy while being downregulated in ischemic cardiomyopathy (figure 4, supplementary figure 1). Suggesting a difference in FAO regulation in different cardiomyopathy types.



Lastly, all papers that show at least one gene associated with FAO to be either up- or down-regulated were selected and compared. Clustering these results, showed some expression patterns (figure 5). For example, *CPT1B*, if detected, is exclusively up-regulated, while on the other hand *DECR1*, is only down-regulated.

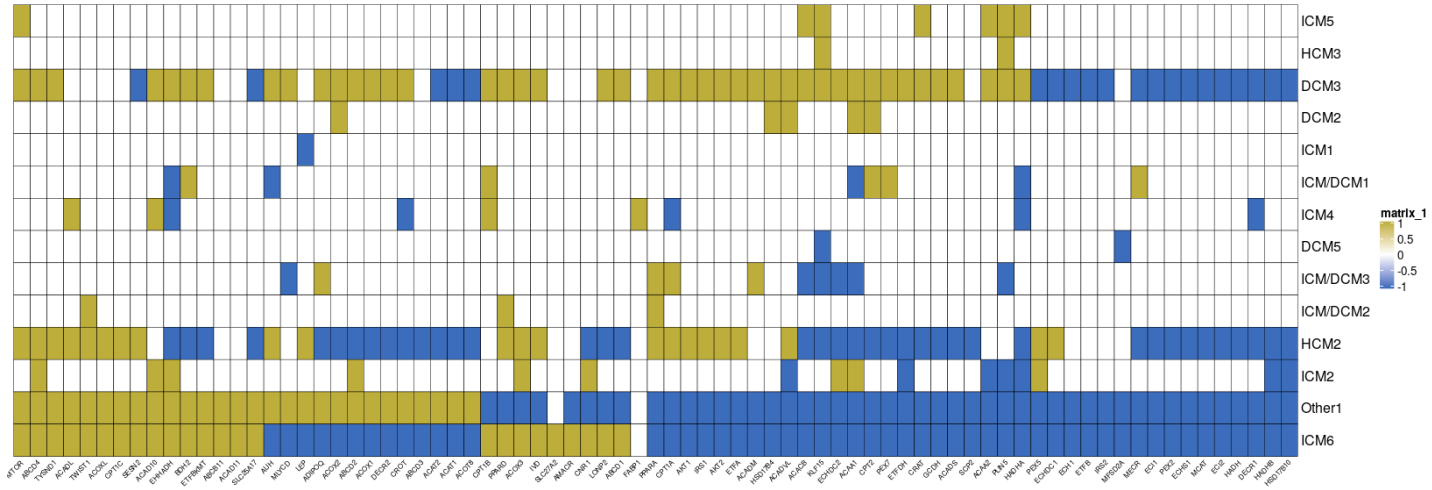


Figure 5. a heatmap of gene expression. *A clustered heatmap showing all genes (x-axis) against all papers (y-axis, supplementary table 3) that found at least one of the 77 genes associated with FAO. The distance for the hierarchical clustering was calculated via the spearman method, both for the rows and columns.*

Discussion

The regulation of FAO is a complex system and the goal of this research was to combine as much data as possible to find some order in this chaos. although the data does not show a clear regulatory pathway, it does make a lot of suggestions. Resulting in the further exploration of genes such as *ACAD10* and *ACAD11* and their regulatory role. Two limiting factors in this research lie in the specificity of the searched research. Only including RNA-seq experiments on human tissue greatly improves the credibility of the results but also results in a significant fall in relevant papers. This is also where the second limiting factor of this paper lies. As can be seen in figure 5, some interesting expression patterns emerge when the up- and down-regulated genes are associated with disease types and are clustered. Only the papers that show DEG associated with FAO are fairly low. Other limitations highlighted in this study are shown in the example in supplementary figure 1. Here one can find genes that in the same type of cardiomyopathy show papers that both show up- and down-regulation of this gene. For example, PLIN5, which is both up- and down-regulated in ICM and DCM. This could be caused by many different things, it could be the age of the patients the sample was taken from. Cardiomyopathy vastly different between young and old patients. It could also be explained by the time point the samples of different experiments were taken, in an early or late stage of cardiomyopathy. Besides these possible factors, it also highlights the messiness of cardiomyopathy research. Although it has been stated that there is already a lot of research done into the expression patterns of cardiomyopathy, here it is shown that the quality of the research differs among papers. Also limiting was the fact that a lot of papers, thought is due to

new GDPR legislation, did not submit their datasets online. Which makes a meta-analysis harder.

In the end, the goal was to generate a dataset that showed the *transcriptional regulation of fatty acid beta-oxidation in public cardiomyopathy datasets.* Combining all these public papers and datasets showed that when large amounts of datasets are combined, some interesting patterns can emerge. Thus showing the importance of researchers publicly submitting their results.

Methods

In this research, multiple search phases were entered, with each phase changing the search criteria to better suit the expected result (figure 1). *1) general insight into lipid metabolism regulation in diseased heart tissue.* To get a general idea of how much research there has been done in the past years, all papers were collected that directly researched the regulation of FAO in cardiomyopathy (figure 1, supplementary table 2). In the processing of finding papers, it was quickly concluded that the majority of papers found were researching into non-human tissue and/or performed a microarray experiment. *2) RNA-seq experiments on lipid metabolism regulation in human tissue.* To get an unbiased and fully translatable result the scope was narrowed down to the exact goal of this research. Looking only for papers that researched the regulation of FAO in humans via an RNA-seq experiment (figure 1, supplementary table 2). We then concluded that this scope was too small. The amount of RNA-seq experiments performed on cardiomyopathy human cells is large enough. Only papers that performed these kinds of experiments and focused mainly on the FAO were low. In total, only four papers were found that investigated the transcriptional regulation of FAO in cardiomyopathy cells via RNA-seq. *3) setting up a gene list and comparing this to a general RNA-seq experiment in diseased human heart tissue*. Many experiments are not focused on only the regulation of fatty acid beta-oxidation or are focused on a completely different topic. However because these are RNA-seq experiments, they test for a whole array of genes and not only the genes their interested in. Most experiments also dump the whole list of deferentially expressed genes as a supplementary figure. this list would be scanned for a subset of genes that are associated with the regulation of fatty acid beta-oxidation. This subset consists of 76 genes found via the gene-ontology term “fatty acid beta-oxidation” and *KLF15* was added, totaling a total of 77 genes. *KLF15* was added because it was recently found that *KLF15* directly interacts with *PPAR-α* and controls the FAO[38].

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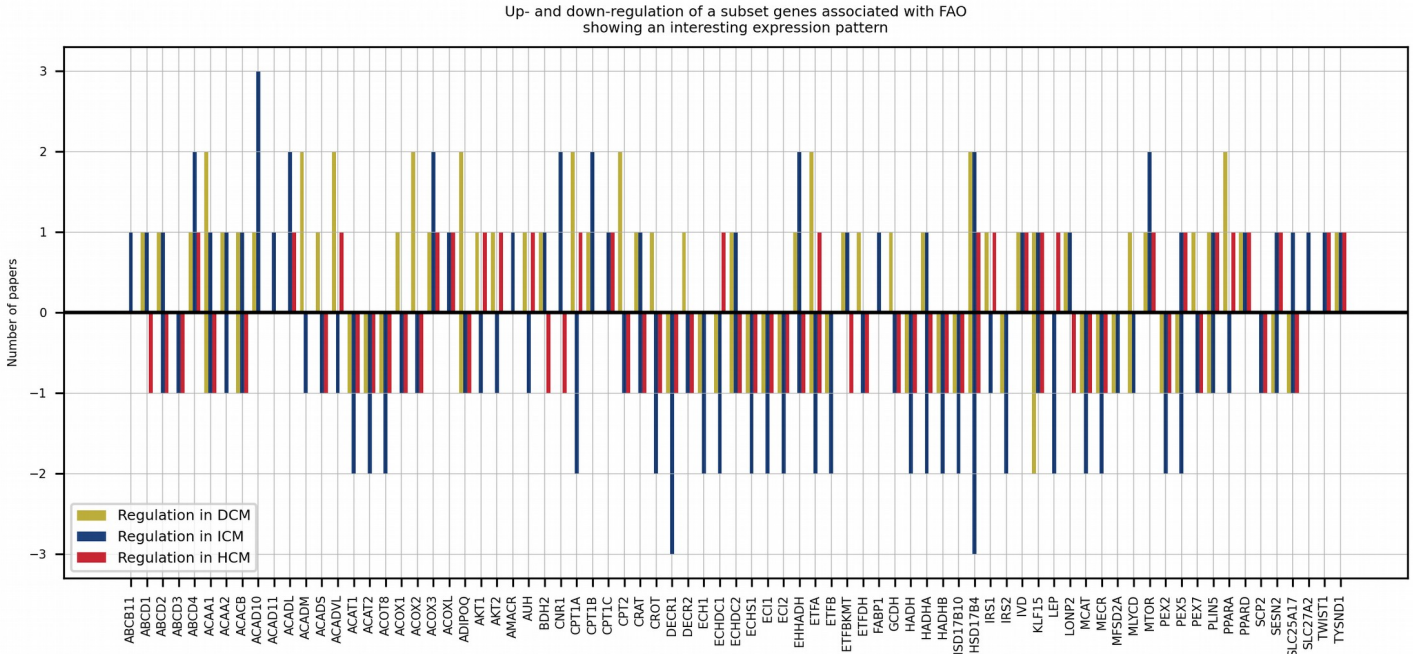
Supplementary material



Supplementary figure 1. *bar graph showing all 77 genes associated with FAO (x-axis) and showing the number of papers (y-axis) reported it being up-regulated (yellow) or down-regulated (blue), split per cardiomyopathy type.*

Supplementary table 1. *table showing some search terms used in different phases of the search process to find papers, together with the number of papers found with this search term.*

Phase 1 - general insight in lipid metabolism regulation in diseased heart tissue	
Search term	**Number of papers found**
"fatty acid beta-oxidation" cardiomyopathy	19.900
cardiomyopathy lipid metabolism genes RNA	49.500
"fatty acid beta-oxidation" (cardiomyopathy OR heart disease) transcription	4.460
transcriptional regulation "fatty acid beta-oxidation" (cardiomyopathy OR heart disease)	5.520
Phase 2 - RNA-seq experiments on lipid metabolism regulation in human tissue	
Search term	**Number of papers found**
(“cardiomyopathy”[Title/Abstract]) AND (“rna-seq”) AND (“human” OR “Patient”) AND (“metabolism”)	10
(“cardiomyopathy”[Title/Abstract]) AND (“rna-seq”) AND (“human” OR “Patient”) AND (“metabolism” OR "oxidation" OR "fatty acid")	11
(“cardiomyopathy” OR "heart disease") AND (“rna-seq”) AND (“metabolism” OR "oxidation" OR "fatty acid")	8.620
cardiomyopathy "rna-seq" (metabolism OR oxidation OR "fatty acid") -mice -rat -rodent	4.0202
Phase 3 - setting up a gene list and comparing this to a general RNA-seq experiment in diseased human heart tissue.	
Search term	**Number of papers found**
cardiomyopathy "rna-seq"	21.400
cardiomyopathy fatty acid oxidation "rna-seq"	11.500
cardiomyopathy DEGS "rna-seq"	8.480
"rna seq" (cardiomyopathy OR heart disease)	36.700
"Single-Cell Transcriptomics" (cardiomyopathy OR "heart disease") metabolism	522
ppar (cardiomyopathy OR "heart disease") "rna-seq"	1.530

Supplementary table 2. *all 77 genes associated with FAO, 76 found in the gene-ontology term GO:0006635, one added via confirmation of multiple papers showing a relation.*

GO:0006635				
Gene stable ID	**Gene name**	**Chromosome**	**Transcript type**	**Synonyms**
ENSG00000073734	ABCB11	2	protein_coding	ABC16, BSEP, PFIC-2, PFIC2, PGY4, SPGP
ENSG00000101986	ABCD1	X	protein_coding	ALD, ALDP, AMN, adrenoleukodystrophy
ENSG00000173208	ABCD2	12	protein_coding	ALDL1, ALDR, ALDRP
ENSG00000117528	ABCD3	1	protein_coding	PMP70, PXMP1, ZWS2
ENSG00000119688	ABCD4	14	protein_coding	EST352188, P70R, PMP69, PXMP1L
ENSG00000060971	ACAA1	3	protein_coding	DSAEC
ENSG00000167315	ACAA2	18	protein_coding	DSAEC
ENSG00000076555	ACACB	12	protein_coding	ACC2, ACCB, HACC275
ENSG00000111271	ACAD10	12	protein_coding	MGC5601
ENSG00000240303	ACAD11	3	protein_coding	FLJ12592
ENSG00000115361	ACADL	2	protein_coding	ACAD4, LCAD
ENSG00000117054	ACADM	1	protein_coding	ACAD1, MCAD, MCADH
ENSG00000122971	ACADS	12	protein_coding	ACAD3, SCAD
ENSG00000072778	ACADVL	17	protein_coding	ACAD6, LCACD, VLCAD
ENSG00000075239	ACAT1	11	protein_coding	ACAT, THIL
ENSG00000120437	ACAT2	6	protein_coding	
ENSG00000101473	ACOT8	20	protein_coding	NAP1, PTE-2, PTE1, hACTE-III, hTE
ENSG00000161533	ACOX1	17	protein_coding	PALMCOX
ENSG00000168306	ACOX2	3	protein_coding	BRCACOX, BRCOX, THCCox
ENSG00000087008	ACOX3	4	protein_coding	
ENSG00000153093	ACOXL	2	protein_coding	FLJ11042
ENSG00000181092	ADIPOQ	3	protein_coding	ACDC, ACRP30, GBP28, adiponectin, apM1
ENSG00000142208	AKT1	14	protein_coding	AKT, PKB, PRKBA, RAC, RAC-alpha
ENSG00000105221	AKT2	19	protein_coding	PKBÎ²
ENSG00000242110	AMACR	5	protein_coding	P504S, RACE
ENSG00000148090	AUH	9	protein_coding	
ENSG00000164039	BDH2	4	protein_coding	DHRS6, FLJ13261, PRO20933, SDR15C1, UCPA-OR, UNQ6308
ENSG00000118432	CNR1	6	protein_coding	CANN6, CB-R, CB1, CB1A, CB1K5, CNR
ENSG00000110090	CPT1A	11	protein_coding	CPT1, CPT1-L, L-CPT1
ENSG00000205560	CPT1B	22	protein_coding	CPT1-M, M-CPT1
ENSG00000169169	CPT1C	19	protein_coding	CPT1P, CPTIC, FLJ23809
ENSG00000157184	CPT2	1	protein_coding	CPT1, CPTASE
ENSG00000095321	CRAT	9	protein_coding	CAT1
ENSG00000005469	CROT	7	protein_coding	COT
ENSG00000104325	DECR1	8	protein_coding	DECR, SDR18C1
ENSG00000242612	DECR2	16	protein_coding	PDCR, SDR17C1
ENSG00000104823	ECH1	19	protein_coding	HPXEL
ENSG00000093144	ECHDC1	6	protein_coding	dJ351K20.2
ENSG00000121310	ECHDC2	1	protein_coding	FLJ10948
ENSG00000127884	ECHS1	10	protein_coding	SCEH
ENSG00000167969	ECI1	16	protein_coding	DCI
ENSG00000198721	ECI2	6	protein_coding	ACBD2, DRS1, HCA88, PECI
ENSG00000113790	EHHADH	3	protein_coding	ECHD
ENSG00000140374	ETFA	15	protein_coding	EMA, GA2, MADD
ENSG00000105379	ETFB	19	protein_coding	
ENSG00000139160	ETFBKMT	12	protein_coding	C12orf72, DKFZp451L235, METTL20, MGC50559
ENSG00000171503	ETFDH	4	protein_coding	ETFQO
ENSG00000163586	FABP1	2	protein_coding	L-FABP
ENSG00000105607	GCDH	19	protein_coding	ACAD5
ENSG00000138796	HADH	4	protein_coding	HADH1, HADHSC, SCHAD
ENSG00000084754	HADHA	2	protein_coding	GBP, LCEH, LCHAD, MTPA
ENSG00000138029	HADHB	2	protein_coding	MTPB
ENSG00000072506	HSD17B10	X	protein_coding	17b-HSD10, ABAD, CAMR, ERAB, HADH2, MHBD, MRPP2, MRXS10, SDR5C1
ENSG00000133835	HSD17B4	5	protein_coding	DBP, MFE-2, SDR8C1
ENSG00000169047	IRS1	2	protein_coding	HIRS-1
ENSG00000185950	IRS2	13	protein_coding	
ENSG00000128928	IVD	15	protein_coding	ACAD2
ENSG00000174697	LEP	7	protein_coding	OB, OBS
ENSG00000102910	LONP2	16	protein_coding	LONP, LONPL, MGC4840
ENSG00000100294	MCAT	22	protein_coding	FASN2C, MCT, MCT1, MT, NET62, fabD
ENSG00000116353	MECR	1	protein_coding	CGI-63, ETR1, FASN2B, NRBF1
ENSG00000168389	MFSD2A	1	protein_coding	FLJ14490, MFSD2
ENSG00000103150	MLYCD	16	protein_coding	MCD, hMCD
ENSG00000198793	MTOR	1	protein_coding	FLJ44809, FRAP, FRAP1, FRAP2, RAFT1, RAPT1
ENSG00000164751	PEX2	8	protein_coding	PAF-1, PMP35, PXMP3, RNF72, ZWS3
ENSG00000139197	PEX5	12	protein_coding	PTS1R, PXR1

ENSG00000112357	PEX7	6	protein_coding	PTS2R, RD
ENSG00000214456	PLIN5	19	protein_coding	LSDA5, LSDP5, MLDP, OXPAT
ENSG00000186951	*PPAR-α*	22	protein_coding	NR1C1, PPAR, hPPAR
ENSG00000112033	PPARD	6	protein_coding	FAAR, NR1C2, NUC1, NUCII
ENSG00000116171	SCP2	1	protein_coding	
ENSG00000130766	SESN2	1	protein_coding	DKFZp761M0212, HI95, SES2, SEST2
ENSG00000100372	SLC25A17	22	protein_coding	PMP34
ENSG00000140284	SLC27A2	15	protein_coding	ACSVL1, FACVL1, FATP2, HsT17226, VLACS, VLCS, hFACVL1
ENSG00000122691	TWIST1	7	protein_coding	ACS3, BPES2, BPES3, CRS, CRS1, H-twist, SCS, TWIST, bHLHa38
ENSG00000156521	TYSND1	10	protein_coding	MGC34695, NET41
Added within research				
Gene stable ID	**Gene name**	**Chromosome**	**Transcript type**	**Synonyms**
ENSG00000163884	KLF15	3	Protein coding	KKLF

Supplementary table 3. *all papers found, with their publishing date and their row name of figure 5 based on the investigated cardiomyopathy type*

Title	year	dissea se
RNA-Seq identifies novel myocardial gene expression signatures of heart failure	2015	ICM/ DCM3
Identification of potential genes for human ischemic cardiomyopathy based on RNA-Seq data	2016	ICM1
RNA-seq profiling of mRNA associated with hypertrophic cardiomyopathy	2016	-
Use of RNA-seq to identify cardiac genes and gene pathways differentially expressed between dogs with and without dilated cardiomyopathy	2016	-
Heart failure: Pilot transcriptomic analysis of cardiac tissue by RNA-sequencing	2017	DCM1
Single cardiomyocyte nuclear transcriptomes reveal a lincRNA-regulated de-differentiation and cell cycle stress-response in vivo	2017	DCM2
Transcriptome analysis of human heart failure reveals dysregulated cell adhesion in dilated cardiomyopathy and activated immune pathways in ischemic heart failure	2018	ICM/ DCM1
CRISPR/Cas9 editing in human pluripotent stem cell-cardiomyocytes highlights arrhythmias, hypocontractility, and energy depletion as potential therapeutic targets for hypertrophic cardiomyopathy	2018	HCM1
Long non-coding and coding RNA profiling using strand-specific RNA-seq in human hypertrophic cardiomyopathy	2019	HCM2
The Translational Landscape of the Human Heart	2019	DCM3
DNA methylation reprograms cardiac metabolic gene expression in end-stage human heart failure	2019	ICM2
Genome-wide DNA methylation encodes cardiac transcriptional reprogramming in human ischemic heart failure	2019	ICM3
Genome-Wide Fetalization of Enhancer Architecture in Heart Disease	2019	DCM5
Epicardial adipose tissue GLP-1 receptor is associated with genes involved in fatty acid oxidation and white-to-brown fat differentiation: A target to modulate cardiovascular risk?	2019	ICM4
Meta-Analysis of Dilated Cardiomyopathy Using Cardiac RNA-Seq Transcriptomic Datasets	2020	DCM4
Identification of Upstream Transcriptional Regulators of Ischemic Cardiomyopathy Using Cardiac RNA-Seq Meta-Analys	2020	ICM5
A Consensus Transcriptional Landscape of Human End-Stage Heart Failure	2020	ICM/ DCM2

Genetic Dissection of Hypertrophic Cardiomyopathy with Myocardial RNA-Seq	2020	HCM3
H3K27ac acetylome signatures reveal the epigenomic reorganization in remodeled non-failing human hearts	2020	-
Transcriptional regulation profiling reveals disrupted lipid metabolism in failing hearts with a pathogenic phospholamban mutation	2020	ICM6