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Journal
Circulation Genomic and Precision Medicine, 5(4)

ISSN
1942-325X

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Publication Date
2012-08-01

DOI
10.1161/circgenetics.111.961912

Peer reviewed

Published in final edited form as:
Circ Cardiovasc Genet. 2012 August 1; 5(4): 422–429. doi:10.1161/CIRCGENETICS.111.961912.

Common Variation in Fatty Acid Genes and Resuscitation from Sudden Cardiac Arrest

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Abstract

Background—Fatty acids provide energy and structural substrates for the heart and brain and may influence resuscitation from sudden cardiac arrest (SCA). We investigated whether genetic variation in fatty acid metabolism pathways was associated with SCA survival.

Methods and Results—Subjects (mean age 67, 80% male, Caucasian) were out-of-hospital SCA patients found in ventricular fibrillation in King County, WA. We compared subjects who survived to hospital admission (n=664) with those who did not (n=689), and subjects who survived to hospital discharge (n=334) with those who did not (n=1019). Associations between survival and genetic variants were assessed using logistic regression adjusting for age, gender, location, time to arrival of paramedics, whether the event was witnessed, and receipt of bystander CPR. Within-gene permutation tests were used to correct for multiple comparisons. Variants in five genes were significantly associated with SCA survival. After correction for multiple comparisons, SNPs in *ACSL1* and *ACSL3* were significantly associated with survival to hospital admission. SNPs in *ACSL3, AGPAT3, MLYCD,* and *SLC27A6* were significantly associated with survival to hospital discharge.

Conclusions—Our findings indicate that variants in genes important in fatty acid metabolism are associated with SCA survival in this population.

Keywords

epidemiology; fatty acids; genetics; heart arrest

Background

Out-of-hospital sudden cardiac arrest (SCA) is a leading cause of death worldwide, accounting for up to 10% of mortality in many countries.[1] In the community, cardiac arrest is often characterized by an initial dysrhythmia of ventricular fibrillation (VF).[2]

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Conflict of Interest Disclosures: None.

Resuscitation is attempted for hundreds of thousands of VF arrest victims worldwide each year, but survival is less than 20% in most communities.[3] Improving outcomes after resuscitation thus has the potential to greatly improve public heath. Some factors related to successful resuscitation have been identified; these include demographic, clinical, and treatment characteristics.[4] However, these factors account for only a moderate proportion of the variance in outcome, indicating that other, as yet unidentified, variables influence the likelihood of resuscitation following VF arrest.[5]

Mortality following SCA is due either to failure to resuscitate the heart or failure of the brain to recover from the ischemic insult. Resuscitation can be viewed as a stepwise process – return of cardiac circulation must occur in the short term, while the process of brain recovery from the injuries caused by reperfusion occurs over a longer period of time. An appreciation of the molecular processes that occur during VF arrest provides a basis for identifying important and novel determinants of cardiac resuscitation and brain recovery. Ventricular fibrillation invokes a time-critical molecular pathophysiology during which there is a substantial modulation of gene expression in both the heart and brain.[6, 7] These time-sensitive mechanisms correspond to significant changes in mRNA and protein levels; modulation of these changes in model organisms has been shown to affect resuscitation.[7–9] Evidence suggests that variation in a number of genes is associated with risk of SCA – family histories of myocardial infarction and sudden cardiac arrest have been associated with an increased risk of out-of-hospital cardiac arrest.[10, 11] In addition, variants in a number of genes have been linked to arrhythmic disorders with a high incidence of sudden cardiac arrest, such as Short QT, Long QT, and Brugada Syndromes.[12, 13] Whether genetic variation influences resuscitation after sudden cardiac arrest, however, remains unknown.

Cellular homeostasis depends in part on fatty acid synthesis and metabolism, processes that are affected by genetic variation.[14, 15] Fatty acids provide integral energy and structural substrates for the heart and brain. These substrates can affect autonomic, vascular, and ischemia/reperfusion pathways, and thus may influence the electric, hemodynamic, and metabolic phases of arrest and resuscitation. Moreover, variation in fatty acid levels or dietary intake has been associated with SCA risk, though little is known about the impact of these factors on resuscitation outcomes.[16] We selected genes from a number of pathways thought to be important in fatty acid synthesis and metabolism for investigation and used a unique biorepository of genetic samples from human subjects who experienced attempted resuscitation from VF cardiac arrest events to assess whether common variation in these genes is associated with successful heart and brain resuscitation.

Methods

Study Design, Population, and Setting

The study cohort is drawn from the population-based Cardiac Arrest Blood Study Repository (CABS-R). CABS-R is a collection of clinical data and biologic specimens from prospectively identified, out-of-hospital cardiac arrest cases age ≥ 18 years, who were attended by paramedics in Seattle and greater King County WA between October 1988 and December 2004, and who had blood drawn in the field. The current study is part of a case-control study of genetic variants and risk of incident SCA. SCA was defined as a sudden pulseless condition in apparently otherwise stable person presumed due to VF in the absence of a non-cardiac cause of arrest. We identified population-based controls of similar age and gender distribution as the cases, who were free of life-threatening non-cardiac conditions and did not suffer SCA.[17–19] The current analyses of resuscitation outcomes focus on potential associations within the case group only; controls were used to check the quality of the genotyping data. The records of 5552 persons identified by emergency medical services (EMS) personnel to be in cardiac arrest were reviewed and classified as definite, probable,

or possible SCA based on initial rhythm (e.g. VF *vs.* asystole), circumstances (e.g. witnessed *vs.* unwitnessed) and possible contribution of comorbidities to the event. As individuals who present with rhythms other than VF (e.g. asystole, pulseless electrical activity (PEA), and ventricular tachycardia) are unlikely to survive and may represent a different underlying pathophysiology, we restricted the population for the current study to the cohort who presented to EMS with an initial rhythm of VF. We further restricted to persons whose events were classified as definite or probable and those of European descent. All nursing home residents were excluded in order to avoid misclassification as to cause of death. The University of Washington Human Subject Review Committee approved the creation and use of repository data and samples for this study. A waiver of consent was granted for all cases who were included.

Clinical Data Sources and Definitions

Clinical covariates and outcomes were obtained from multiple sources, including EMS incident reports, death certificates, and hospital records for those patients who survived to hospital admission. We used Utstein definitions to classify demographic, circumstance, and treatment characteristics.[20] We defined two distinct outcomes prior to data analysis to represent cardiac and brain resuscitation. Cardiac resuscitation was defined as return of spontaneous circulation that enabled admission to the hospital. Brain resuscitation was defined as survival to hospital discharge.

Blood collection

Paramedics obtained blood specimens from cases in the field after emergency medical care had been provided and either the patient was clinically stable or declared dead. Blood was collected in tubes containing EDTA, and DNA was extracted from white blood cells using standard phenol extraction procedures.

Gene and SNP Selection

We included a total of 41 genes thought to be involved in fatty acid synthesis and metabolism that we hypothesized might also be related to SCA risk and the likelihood of survival (Table 1). For each gene, we identified single nucleotide polymorphisms (SNPs) that captured, or tagged, common patterns of variation across the gene using information from the Genome Variation Server (GVS) (http://gvs.gs.washington.edu/GVS/index.jsp) and the International HapMap Project (http://hapmap.org). Data for common variants (minor allele frequency (MAF) ≥ 0.05) in European populations (GVS:PGA_CEPH; HapMap:CEU) for each gene and for 500 base pairs on either side of the gene were downloaded. For genes where data were obtained from HapMap, the Tagger pairwise algorithm was used to select tagSNPs ($r^2 \geq 0.80$).[21] For genes where data were obtained from GVS, the LDSelect algorithm was used to select tagSNPs ($r^2 \geq 0.80$).[22] In addition, we selected coding non-synonymous (CNS) SNPs with MAF ≥0.01 in dbSNP (http://www.ncbi.nlm.nih.gov/snp) and SNPs of particular interest based on literature reviews. Details about the selected and genotyped SNPs, including their genomic context, MAF, major and minor alleles, and regression results, can be found in the Supplemental Table.

Ancestry

Ancestry was defined by death certificate information, or by hospital data or EMS information if the patient was still alive. We also genotyped 93 SNPs identified as ancestry informative markers in the Multi-Ethnic Study of Atherosclerosis to confirm reported ancestry.[23] These SNPs were used to calculate principal components which were then used

to identify outliers among subjects who were identified as white or for whom we had no information about race.[24]

Genotyping

Genotyping was performed by the Kwok Lab at UCSF (Kwok, Department of Biopharmaceutical Sciences UCSF; San Francisco CA) using BeadArray technology with a custom GoldenGate panel (Illumina, San Diego, CA).

Statistical methods

Analyses were carried out using Stata 11.0 (StataCorp, College Station TX). We tabulated descriptive statistics for covariates, including age, gender, location of arrest, time from 911 call to arrival of EMS, number of shocks received, whether the arrest was witnessed, whether bystander cardiopulmonary resuscitation (CPR) was administered, and whether EMS arrival preceded cardiac arrest.

Hardy-Weinberg equilibrium for each SNP was assessed among control participants using an exact test.[25] SNPs with p-values below 0.01 were excluded from the analyses. We examined the degree of linkage disequilibrium (LD) between the variants using r^2.[26]

Genotype-resuscitation associations were assessed using logistic regression with robust or 'sandwich' standard errors to obtain odds ratios (OR) and their 95% confidence intervals. These regressions adjusted for age category (≤40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75, ≥76), gender, time from 911 call to scene arrival of EMS (0–5, 5–10, 10+ minutes), whether the event was witnessed, whether the event occurred in public, and whether the arrest victim received bystander CPR.[27] Time to EMS arrival categories were based on previous work indicating time intervals associated with survival.[28] An additive model (0=common homozygote, 1=heterozygote, 2=rare homozygote) was used for all SNPs. Separate analyses were performed for the outcomes of survival to hospital admission (cardiac resuscitation) and survival to hospital discharge (brain resuscitation). Robust standard errors were used to ensure large-sample validity of the estimated standard errors.

The permutation-based p-min procedure and a Holm step-down procedure were used to adjust for multiple comparisons of the correlated SNPs within a gene.[29] Specifically, we randomly permuted case-control status within strata defined by the model covariates 10,000 times to obtain a corrected two-sided p-value for each SNP.

We performed sensitivity analyses adjusted for ancestry using eight principal components derived from ancestry informative markers to control for potential residual population stratification.

Five hundred sixty-three SNPs in 41 genes involved in fatty acid metabolism were genotyped in 1458 subjects. Samples from 37 cases (2.5%) had call rates <90% and were excluded from analysis. Six subjects (0.4%) were identified as gender mismatches based on analysis of X-linked SNPs and were excluded from analysis. Eleven subjects (0.8%) were identified as non-European by ancestry informative markers and were excluded from analysis. Fifty-one subjects (3.5%) were missing data on covariates and were thus excluded from the analysis. Eighty-five (15.1%) of the 563 SNPs failed genotyping due to poor clustering, low call rate (<95%), or were out of Hardy-Weinberg equilibrium in controls ($p<0.01$) and were excluded from analysis. Thirty-nine (6.9%) SNPs were monomorphic and were also excluded. All SNPs in ELOVL1 were excluded – 2 SNPs were monomorphic and 3 failed to generate clusters during the genotype calling process. Thus, in the current investigation, we evaluated data on 439 SNPs in 40 genes from 1353 SCA case subjects.

Results

Of the 1353 SCA victims who presented with VF as their initial rhythm, 689 (50.9%) died in the field, while 330 (24.4%) died in the hospital, and 334 (24.7%) survived to hospital discharge. The average age of subjects was 67, the majority (80.3%) were men, and most (75.8%) events were witnessed. As expected, those with successful heart and brain resuscitation tended to be younger, have a witnessed arrest, receive bystander CPR and require fewer shocks (Table 2).

Six SNPs in 5 genes were associated with either survival to hospital admission or survival to hospital discharge after correction for multiple comparisons. One SNP, rs1014280 (*ACSL3*), was associated with both outcomes.

Acetyl-CoA Synthetases

ACSL1—The G allele of rs4862419 (MAF 0.17, intron) was negatively associated with survival to hospital admission (OR (95% CI): 0.74 (0.60, 0.91), corrected p=0.029). This SNP was not significantly associated with survival to hospital discharge (Table 3). No other SNPs in this gene were significantly associated with either survival to hospital admission or survival to hospital discharge after correction for multiple comparisons (data not shown).

ACSL3—The A allele of rs1014280 (MAF 0.33, intron) was negatively associated with both survival to hospital admission (OR (95% CI): 0.77 (0.65, 0.91), corrected p=0.038) and survival to hospital discharge (OR (95% CI): 0.73 (0.59, 0.89), corrected p=0.021). The G allele of rs795891 (MAF 0.19, intron) was positively associated with survival to hospital discharge (OR (95% CI): 1.37 (1.09, 1.72), corrected p=0.042). This variant was also positively associated with survival to hospital admission, but the association did not remain statistically significant after correction for multiple comparisons (OR (95% CI): 1.25 (1.02, 1.53), corrected p=0.232) (Table 3). These two SNPs are in mild linkage disequilibrium (r^2=0.10).

Acyl-glycerol-phosphate-O-acyltransferases

AGPAT3—The G allele of rs4819351 (MAF 0.21, intron) was positively associated with survival to hospital discharge (OR (95% CI): 1.49 (1.19, 1.86), corrected p=0.011). No SNPs were significantly associated with survival to hospital admission after correction for multiple comparisons (Table 3).

Malonyl-CoA decarboxylase

MLYCD—The G allele of rs11649200 (MAF 0.15, intron) was negatively associated with survival to hospital discharge (OR (95% CI): 0.73 (0.57, 0.94), corrected p=0.041). This variant was not significantly associated with survival to hospital admission (Table 3). No SNPs in this gene were significantly associated with survival to hospital admission.

Solute Carrier Family 27 Transporter

SLC27A6—The G allele of rs2526247 (MAF=0.37, missense L19V) was negatively associated with survival to hospital discharge (OR (95% CI): 0.77 (0.64, 0.93), corrected p=0.049). This variant was also associated with a decreased likelihood of survival to hospital discharge (OR (95% CI): 0.84 (0.72, 0.98), corrected p=0.323), but this second result did not remain significant after correction for multiple comparisons (Table 3).

Sensitivity Analyses

Results for all analyses were similar when we included adjustment for ancestry derived from the genotyped ancestry informative markers in the models.

Discussion

In most communities, survival rates following out-of-hospital cardiac arrest are poor. While known predictors of successful resuscitation point to changes in emergency care systems that may improve outcomes in some communities, additional work is needed to identify other factors that influence the likelihood of survival.[4] Because fatty acids are integral energy and structural substrates of the heart and brain, we evaluated whether common variation in 40 genes involved in fatty acid transport and metabolism was associated with heart and brain resuscitation. We found that 6 common variants in 5 genes (*ACSL1, ACSL3, AGPAT3, MLYCD*, and *SLC27A6*) that regulate important aspects of fatty acid metabolism are associated with resuscitation outcomes (Figure 1). Our results not only suggest that fatty acid metabolism may have an influential role in resuscitation, but also provide potential insight into the responsible mechanisms.

Successful resuscitation of sudden cardiac arrest requires early cardiac resuscitation followed by brain recovery. Thus the initial stage of resuscitation primarily involves the heart while favorable long-term clinical outcome measured by survival to hospital discharge incorporates both the heart and the brain. From a physiological perspective, long-term survival requires that one overcome the initial ischemia and then tolerate the adverse effects of reperfusion, including inflammation and the production of reactive oxidant species. In the normal heart, fatty acid oxidation is responsible for 60–90% of the ATP needed for cardiac function.[30] During periods of ischemia, fatty acid and glucose oxidation pathways become dysregulated, leading to the accumulation of metabolic intermediates and inefficient use of ATP. Reduction of fatty acid oxidation and an increase in glucose oxidation are associated with improved recovery of the heart after ischemia/reperfusion injury in animal models.[31, 32] While the brain primarily uses glucose as an energy source, fatty acids are important in cell membrane integrity and various physiological processes including apoptosis, gene transcription, and signaling.[33, 34] During periods of ischemia, there is a marked accumulation of free fatty acids due to activation of lipases, including membrane phospholipases, phospholipase C, diglyceride lipase, and lysophospholipase.[35] Free fatty acids contribute to neuronal death by inducing apoptosis and necrosis via generation of reactive oxygen species, *de novo* ceramide synthesis, production of nitric oxide, and mitochondrial dysfunction.[36] In both the heart and brain, these fatty acids are reincorporated into membrane phospholipids via an ATP-dependent mechanism involving acyl-CoA intermediates during reperfusion.[37] In animal models, fatty acids and their derivatives have also been shown to mediate ischemic pre- and postconditioning, processes shown to reduce infarct size and improve resuscitation outcomes.[38] While it is possible that the genes we found to be associated with resuscitation outcomes may influence these processes, elucidating the mechanisms of these changes will require further studies.

Fatty acid transport proteins (FATP/SLC27A family) are transmembrane proteins that enhance long-chain fatty acid uptake into cells.[39] SLC27A6 is the major isoform in the heart.[40] In agreement with a functional role, overexpression of mammalian *SLC27A6* has been reported to increase fatty acid uptake.[41] rs2526247, which was associated with the likelihood of survival to hospital discharge in the current study, is a coding non-synonymous SNP that results in an amino acid change from leucine to valine at residue 19. While the functional consequence of this change is unknown, an analogous SNP in the SLC27A1 isoform indicates that this residue is located in the region responsible for membrane association.[39] The two isoforms share a similar overall structure and organization of

domains, and we hypothesize that rs2526247 may affect membrane integration and thus transporter function.[41]

Acyl-CoA synthetases (ACSL) activate free long-chain fatty acids by converting them into fatty acyl-coenzyme A (CoA) esters. These enzymes may act in concert with transport proteins to regulate fatty acid transport into cells. For example, ACSL enzymes interact with SLC27A1 in mouse Leydig cells and adipocytes.[41] Fatty acyl-CoA esters are substrates for multiple fatty acid metabolic pathways, including mitochondrial beta-oxidation and phospholipid and triacylglycerol synthesis.[42, 43] Analysis of expression patterns in rat hearts indicates that both ACSL1 and ACSL3 contribute to fatty acid metabolism in the heart; ACSL3 is also found in brain tissue.[42] While the functional consequences of the SNPs are not known, the present study suggests that genetic variation influences heart (*ACSL1* and *ACSL3*) and brain (*ACSL3*) resuscitation. Variation in ACSL enzymes may affect cellular or mitochondrial energy stores and thus may influence vulnerability to the oxidative stress inherent in arrest and resuscitation. Alternatively these variants may affect the availability of long-chain fatty acid acyl-CoA substrates and thus influence rates of free fatty acid reincorporation into membrane phospholipids.[44]

Malonyl CoA is an endogenous regulator of fatty acid oxidation – it inhibits the carnitine transferase pathways, turning off fatty acid-CoA transport into the mitochondria and fatty acid beta-oxidation. Malonyl CoA is degraded by malonyl CoA decarboxylase (*MLYCD*). In mouse and rat models, inhibition of *MLYCD* lead to reduced rates of fatty acid oxidation and increased rates of glucose oxidation.[45] Cardiac malonyl CoA levels decrease rapidly during ischemia/reperfusion leading to upregulation of fatty acid oxidation with concomitant reduction in glucose oxidation. *In vitro* and animal work suggest that altering the levels of malonyl CoA in the heart may optimize cardiac metabolism during periods of ischemia, but there is limited data on the effectiveness of this approach in humans.[45] While beta oxidation of fatty acids is a minor pathway in the brain, changes in the regulation of this pathway may alter the kinetics of removing free fatty acids from brain cells, thus affecting the damage done to these cells during ischemia/reperfusion. Our results suggest that variation in *MLYCD* influences resuscitation from cardiac arrest; we speculate that this may be due an effect of the levels of malonyl CoA.

Members of the lysophosphatidic acid acyltransferase (AGPAT) family convert lysophosphatidic acid into phosphatidic acid, a key step in various processes, including *de novo* phospholipid synthesis (Kennedy pathway), triacylglycerol synthesis, and reacylation of existing lysophospholipids (Lands cycle, Figure 1).[46] While acyltransferase activity has been extensively studied in cell culture and animal models, little is known specifically about AGPAT3 activity in humans. Data from cells transfected with human AGPAT3 indicate that it is localized to the endoplasmic reticulum and Golgi complex where it is involved in phospholipid remodeling.[47] Other data suggest that AGPAT activity may affect endogenous triacylglycerol stores, which provide up to 50% of the fatty acid substrates for beta-oxidation and ATP generation.[43, 48] Turnover of endogenous triacylglyceride stores has been shown to be accelerated during ischemia.[49] The effects of this increase are mixed – unnecessary triacylglyceride turnover wastes ATP, but also reduces cytosolic accumulation of free fatty acids and their intermediates that have been shown to be cardiotoxic at high levels.[49] In addition, phosphatidic acid is a key intermediate in membrane phospholipid synthesis, and thus changes in enzymatic function may affect the rate of reincorporation of free fatty acids during reperfusion.[50]

This study has certain strengths and limitations. While the study cohort was prospectively identified and drawn from the general population, eligibility required that paramedics draw blood for DNA collection. We thus have incomplete case ascertainment (approximately 33%

of potentially eligible patients had blood collected) either because the EMS system was not activated, or because the requirements of patient care prevented the paramedics from obtaining a blood sample. However, the characteristics and outcomes in the current study population are similar to other reports of VF cardiac arrests from the study community and to other VF arrest cohorts.[1, 51] The study community is served by a mature EMS system where survival is high relative to many communities. We do not know, however, whether EMS care modifies the relationship between genetic variation and outcome. We used operational definitions to define cardiac and brain resuscitation, but did not directly assess cerebral function after the arrest. While survival to hospital admission solely reflects cardiac resuscitation, survival to hospital discharge is a more complicated phenotype that reflects successful cardiac and brain resuscitation. These outcomes were selected to achieve a practicable balance of scientific relevance, clinical importance, and measurable validity; while analyses using survival to hospital admission as the outcome measure may provide clues as to mechanism, survival to hospital discharge for all patients is the ultimate goal.

The current study is limited to persons of European descent and our findings may not generalize to populations of other racial/ethnic backgrounds. Even among European Americans, population stratification can confound associations, but we addressed this concern by adjusting for principal components derived from ancestry informative markers. False positive associations are also a concern in genetic association studies, but our permutation-based inference limits our expected number of these errors. Without independent replication, these results should be viewed as suggestive of an association rather than definite evidence; however, the unique biorepository required to undertake this investigation meant that no validation population was available.

We also excluded patients who presented to EMS with an initial rhythm other than VF, thus our results are not generalizable to persons found in asystole, PEA, and ventricular tachycardia.

In this population-based cohort study of out-of-hospital VF arrest due to heart disease, we found that common variation in genes that regulate fatty acid transport and metabolism is associated with cardiac and brain resuscitation outcomes. The results provide better understanding of how fatty acid metabolism may influence resuscitation outcomes. Ultimately, improved understanding may direct developments in treatment for cardiac arrest that could improve public health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: This study was financed by the National Lung, Heart, and Blood Institute. RO1-HL088576, RO1-HL092144, RO1-HL088456.

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Out-of-hospital sudden cardiac arrest (SCA) is a leading cause of death worldwide, accounting for up to 10% of mortality in many countries; the presenting rhythm is frequently ventricular fibrillation (VF). Resuscitation is attempted for hundreds of thousands of VF arrest victims worldwide each year; however, survival is less than 20% in most communities. While factors related to successful resuscitation have been identified, they account for only a moderate proportion of variance in the outcome, indicating that other, as yet unidentified, variables influence the likelihood of resuscitation. Improving our understanding of factors influencing resuscitation thus has the potential to greatly improve public heath. Survival from SCA is dependent on the ability of the heart and brain to withstand the effects of ischemia/reperfusion injury. Re-establishment of cellular homeostasis after cardiac arrest depends in part on fatty acid synthesis and metabolism, processes that are affected by genetic variation. Fatty acids provide integral energy and structural substrates for the heart and brain. These substrates can affect autonomic, vascular, and ischemia/reperfusion pathways, and thus may influence arrest and resuscitation. Moreover, variation in fatty acid levels or dietary intake has been associated with SCA risk. We found that variants in *ACSL1* and ACSL3 were significantly associated with survival to hospital admission, while variants in *ACSL3, AGPAT3*, *MLYCD*, and *SLC27A6* were significantly associated with survival to hospital discharge. These findings indicate that fatty acid metabolism likely plays a role in survival from VF arrest; further follow-up of these findings is needed.

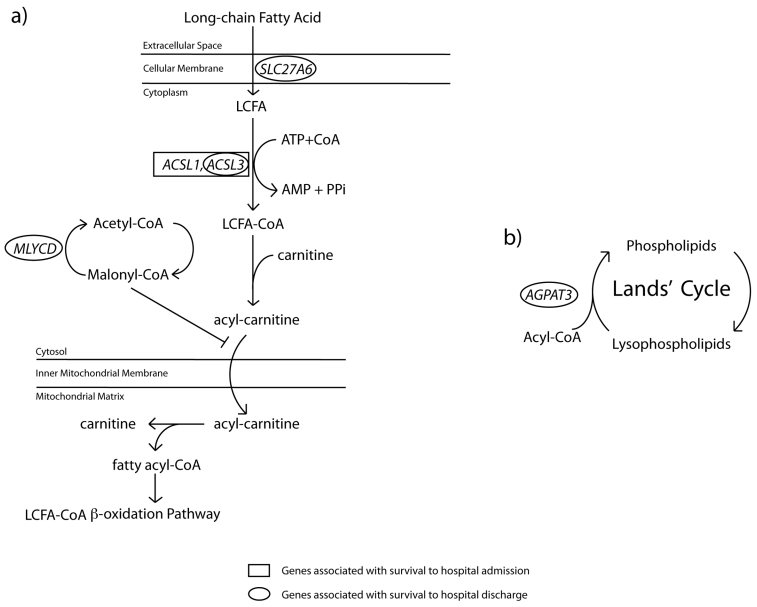

Figure 1.

Genes Associated with Outcomes in the Context of Two Fatty Acid Metabolism Pathways**.** **a**) Influx of Fatty Acids and Regulation of beta-Oxidation: *SLC27A6* – transports fatty acids into cells; *ACSL1, ACSL3* – converts long-chain fatty acids into fatty acyl-CoA esters, capturing them in the cell; *MLYCD* – catalyzes the breakdown of malonyl-CoA, a key regulator of fatty acid beta-oxidation that inhibits the transport of fatty acyl CoAs into mitochondria. **b**) Acylation/Reacylation Pathway (Lands' Cycle): *AGPAT3* – reacylates the sn1 position of lysophospholipids

Table 1

Numbers of SNPs Assayed and Passing Quality-Control Filters for Analysis in Candidate Fatty Acid Genes

Gene	Gene Name	SNPs Typed	SNPs Analyzed
ACACA	Acetyl-CoA carboxylase alpha	17	15
ACACB	Acetyl-CoA carboxylase beta	33	26
ACSL1	Acyl-CoA synthetase long-chain family member 1	19	14
ACSL3	Acyl-CoA synthetase long-chain family member 3	15	10
ACSL4	Acyl-CoA synthetase long-chain family member 4	4	3
ACSL5	Acyl-CoA synthetase long-chain family member 5	14	10
ACSS1	Acyl-CoA synthetase short-chain family member 1	15	10
ACSS2	Acyl-CoA synthetase short-chain family member 2	5	4
AGPAT1	1-acylglycerol-3-phosphate O-acyltransferase 1	6	4
AGPAT2	1-acylglycerol-3-phosphate O-acyltransferase 2	7	4
AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3	27	21
AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4	48	42
CD36	CD36 molecule (thrombospondin receptor)	12	11
CPT1B	Carnitine palmitoyltransferase 1B	11	10
CPT2	Carnitine palmitoyltransferase 2	4	4
CRAT	Carnitine O-acetyltransferase	5	3
ELOVL1	Elongation of very long chain fatty acids 1	5	0
ELOVL4	Elongation of very long chain fatty acids 4	4	4
ELOVL5	Elongation of very long chain fatty acids 5	11	9
ELOVL6	Elongation of very long chain fatty acids 6	41	36
FABP3	Fatty acid binding protein 3	6	6
FADS1	Fatty acid desaturase 1	4	1
FADS2	Fatty acid desaturase 2	13	13
FADS3	Fatty acid desaturase 3	5	3
FASN	Fatty acid synthase	10	3
INSIG1	Insulin induced gene 1	6	2
LPCAT1	Lysophosphatidylcholine acyltransferase 1	33	27
LPGAT1	Lysophosphatidylglycerol acyltransferase 1	11	9
LPL	Lipoprotein lipase	17	13
MLYCD	Malonyl-CoA decarboxylase	8	7
PLA2G4C	Phospholipase A2, group IVC	23	20

Gene	Gene Name	SNPs Typed	SNPs Analyzed
PNPLA8	Patatin-like phospholipase domain containing 8	8	5
SCAP	SREBF chaperone	7	2
SCD5	Stearoyl-CoA desaturase 5	51	46
SLC25A20	Solute carrier family 25 (carnitine/acylcarnitine translocase), member 20	3	3
SLC27A1	Solute carrier family 27 (fatty acid transporter), member 1	7	7
SLC27A3	Solute carrier family 27 (fatty acid transporter), member 3	5	3
SLC27A4	Solute carrier family 27 (fatty acid transporter), member 4	4	1
SLC27A6	Solute carrier family 27 (fatty acid transporter), member 6	17	13
SREBF1	Sterol regulatory element binding transcription factor 1	7	4
SREBF2	Sterol regulatory element binding transcription factor 2	15	11

Table 2

Selected Characteristics of Subjects by Survival Status

Covariate	All Subjects [n=1353]	Died in Field [n=689]	Admitted to Hospital [n=664]†	Discharged Alive [n=334]†
Female	266 (19.7%)	123 (17.9%)	143 (21.5%)	72 (21.6%)
Age (years)	67.2 (13.8)	67.4 (14.0)	67.0 (13.6)	63.8 (13.9)
Arrest Occurred at Home	818 (60.5%)	453 (65.7%)	365 (55.0%)	150 (44.9%)
Arrest Witnessed	1026 (75.8%)	468 (67.9%)	558 (84.0%)	297 (88.9%)
Bystander CPR Administered	836 (61.8%)	413 (59.9%)	423 (63.7%)	232 (69.5%)
Time to EMS Arrival (min)	4.9 (2.1)	5.1 (2.1)	4.7 (2.1)	4.2 (1.8)
Number of Shocks Received*	5 (2,8)	6 (3, 9)	4 (2, 7)	3 (1, 5)
EMS Arrival Preceded Arrest	57 (4.2%)	25 (3.6%)	32 (4.8%)	26 (7.8%)

*Median (IQR), else N(%) or Mean(SD)

†Subjects who were discharged alive are included in the Admitted to Hospital group

Table 3

Association Results for Genes and SNPs Significantly Related to Survival to Hospital Admission or Hospital Discharge

Gene	rsnumber	MAF	Alleles*	Context	Model	OR (95% CI)†	Standard Error	p-value Uncorrected	p-value Corrected‡
ACSL1	rs4862419	0.17	G/A	Intron	Admission	0.74 (0.60, 0.91)	0.107	0.005	0.029
					Discharge	0.84 (0.65, 1.09)	0.132	0.188	0.646
ACSL3	rs1014280	0.33	A/G	Intron	Admission	0.77 (0.65, 0.91)	0.087	0.002	0.038
					Discharge	0.73 (0.59, 0.89)	0.106	0.003	0.021
	rs795891	0.19	G/A	Intron	Admission	1.25 (1.02, 1.53)	0.103	0.033	0.232
					Discharge	1.37 (1.09, 1.72)	0.116	0.007	0.042
AGPAT3	rs4819351	0.21	G/A	Intron	Admission	1.22 (1.01, 1.48)	0.098	0.041	0.366
					Discharge	1.49 (1.19, 1.86)	0.115	0.001	0.011
MLYCD	rs11649200	0.15	A/G	Intron	Admission	0.96 (0.78, 1.19)	0.109	0.728	0.922
					Discharge	0.73 (0.57, 0.94)	0.129	0.014	0.041
SLC27A6	rs2526247	0.37	T/G	Missense, L19V	Admission	0.84 (0.72, 0.98)	0.079	0.027	0.323
					Discharge	0.77 (0.64, 0.93)	0.096	0.006	0.049

*Major/Minor Allele

†SNPs coded using an additive model (0=common homozygote, 1=heterozygote, 2=rare homozygote)

‡Corrected for multiple comparisons