

## Prospective Study

# Genotype specific peripheral lipid profile changes with hepatitis C therapy

Mark R Pedersen, Amit Patel, David Backstedt, Myunghan Choi, Anil B Seetharam

Mark R Pedersen, Department of Internal Medicine, Banner University Medical Center, University of Arizona College of Medicine, Phoenix, AZ 85006, United States

Amit Patel, David Backstedt, Department of Gastroenterology, Banner University Medical Center, University of Arizona College of Medicine, Phoenix, AZ 85006, United States

Myunghan Choi, Arizona State University College of Nursing and Health Care Innovation, Phoenix, AZ 85006, United States

Anil B Seetharam, Banner Transplant and Advanced Liver Disease Center, University of Arizona College of Medicine, Phoenix, AZ 85006, United States

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**Correspondence to:** Anil B Seetharam, MD, Banner Transplant and Advanced Liver Disease Center, University of Arizona College of Medicine, 1300 N. 12<sup>th</sup> Street Suite 404, Phoenix, AZ 85006, United States. [anil.seetharam@bannerhealth.com](mailto:anil.seetharam@bannerhealth.com)  
Telephone: +1-602-8397000  
Fax: +1-602-8397050

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## Abstract

### AIM

To evaluate magnitude/direction of changes in peripheral lipid profiles in patients undergoing direct acting therapy for hepatitis C by genotype.

### METHODS

Mono-infected patients with hepatitis C were treated with guideline-based DAAs at a university-based liver clinic. Patient characteristics and laboratory values were collected before and after the treatment period. Baseline demographics included age, ethnicity, hypertension, diabetes, hyperlipidemia, treatment regimen, and fibrosis stage. Total cholesterol (TCHOL), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), and liver function tests were measured prior to treatment and ETR. Changes in lipid and liver function were evaluated by subgroups with respect to genotype. Mean differences were calculated for each lipid profile and liver function component (direction/magnitude). The mean differences in lipid profiles were then compared between genotypes for differences in direction/magnitude. Lipid profile and liver function changes were evaluated with Levene's test and student's *t* test. Mean differences in lipid profiles

were compared between genotypes using ANOVA, *post hoc* analysis *via* the Bonferroni correction or Dunnett T3.

## RESULTS

Three hundred and seventy five patients enrolled with 321 (85.6%) achieving sustained-viral response at 12 wk. 72.3% were genotype 1 (GT1), 18.1% genotype 2 (GT2), 9.7% genotype 3 (GT3). Baseline demographics were similar. Significant change in lipid profiles were seen with GT1 and GT3 ( $\Delta$ GT1, *p* and  $\Delta$ GT3, *p*), with TCHOL increasing (+5.3, *P* = 0.005 and +16.1, *P* < 0.001), HDL increasing (+12.5, *P* < 0.001 and +7.9, *P* = 0.038), LDL increasing (+7.4, *P* = 0.058 and +12.5, *P* < 0.001), and TG decreasing (-5.9, *P* = 0.044 and -9.80, *P* = 0.067). Among genotypes ( $\Delta$ GT1 v.  $\Delta$ GT2 v.  $\Delta$ GT3, ANOVA), significant mean differences were seen with TCHOL (+5.3 v. +0.1 v. +16.1, *P* = 0.017) and HDL (+12.3 v. +2 v. +7.9, *P* = 0.040). Post-hoc, GT3 was associated with a greater increase in TCHOL than GT1 and GT2 (*P* = 0.028 and *P* = 0.019).

## CONCLUSION

Successful DAA therapy results in increases in TCHOL, LDL, and HDL and decrease in TG, particularly in GT1/GT3. Changes are most pronounced in GT3.

**Key words:** Hepatitis C genotypes; Lipids; Metabolic syndrome

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**Core tip:** Different genotypes of the hepatitis C virus (HCV) are associated with differing levels of hepatic steatosis, with genotype 3 (GT3) having the strongest direct association. In this investigation, change in peripheral lipid panels during direct-acting antiviral therapy were assessed in a large HCV treatment cohort with respect to genotype. Total cholesterol in patients with GT3 increased significantly during treatment compared to other genotypes. Associated steatosis and differing lipid kinetics may influence response rates to direct acting therapy and may also influence genotype specific risks of hepatic and systemic complications.

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## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is associated with hepatic steatosis and hypocholesterolemia<sup>[1]</sup>. HCV utilizes peripheral lipid metabolism pathways including hepatocyte very-low-density lipoprotein for viral assembly and requires several apolipoproteins

for production of infective particles<sup>[2,3]</sup>. Chronic HCV increases levels of hepatic steatosis independent of other classical risk factors for non-alcoholic fatty liver disease<sup>[1]</sup>. The magnitude of this effect varies by genotype. Genotype 3 (GT3) in particular is associated with a primary hepatic steatosis that appears to correlate directly with viral load while genotype 1 (GT1) and 2 (GT2) have less pronounced secondary steatosis related to increased insulin resistance and body mass index<sup>[1-3]</sup>.

Successful clearance of HCV viremia with immunomodulatory therapy (pegylated interferon and ribavirin) has been associated with a rise in serum total cholesterol (TCHOL) and low density lipoprotein (LDL)<sup>[4]</sup>. In the post-interferon era, Meissner *et al*<sup>[5]</sup> demonstrated that patients with chronic HCV GT1 treated with sofosbuvir and ribavirin had increases in their serum LDL and decrease in serum triglyceride (TG).

Peripheral lipid profile changes during treatment for non-genotype 1 infection with DAA therapy are thus far uncharacterized. The purpose of this study was to examine effects of DAA therapy on serum TCHOL and peripheral lipid components and evaluate differences in responses among HCV genotypes.

## MATERIALS AND METHODS

### Ethical considerations

This study was reviewed and approved by the Banner University Medical Center - Phoenix Institutional Review Board. While data was collected prospectively, all patients were monitored in accordance with American Association for the Study of Liver Disease and Infectious Diseases Society of America hepatitis C guidelines. As there was no deviation from standard of care, need for informed consent for the prospective study was waived by the institutional review board.

### Study design

We performed a prospective cohort study of consecutively-enrolled mono-infected HCV patients achieving sustained virologic response at 12 wk (SVR12) treated at Banner University of Arizona Medical Center in Phoenix, Arizona from January 2014 to November 2015. After institutional review board approval, outpatient medical records were reviewed and variables of interest tabulated.

### Treatment regimens

All patients were treated according to the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America guidelines active at the time of treatment initiation. Consecutively enrolled subjects received one of the following treatment regimens: pegylated Interferon alfa 2a + sofosbuvir + ribavirin; sofosbuvir + ribavirin; sofosbuvir + simeprevir; or ledipasvir + sofosbuvir. When applicable, ribavirin was dosed by weight, 1000 mg total daily dose if weight < 75 kg or 1200 mg total daily dose if > 75 kg.

### Baseline demographics

Baseline demographics were recorded prior (within 30 d prior) to regimen initiation including: age, ethnicity, treatment regimen, and fibrosis stage as well as the presence of hypertension, diabetes, and hyperlipidemia prior to treatment. Liver function tests [including alanine aminotransferase (ALT), total bilirubin, and albumin] as well as the protime/International Normalized Ratio (INR) were recorded before and after treatment. Fibrosis stage was assessed *via* FibroSure serum testing (Laboratory Corporation of American, Herdon, Virginia) or liver biopsy. Presence of hypertension, diabetes, and hyperlipidemia prior to treatment was determined based on documentation of formal diagnosis in the medical record and concomitant medications regimens indicative of the diagnosis (e.g., insulin use was considered indicative of diabetes). Medication lists were monitored prior to and after the end of treatment for any new or discontinued medications.

### Metabolic measurements

Per protocol in the Liver Clinic at Banner University of Arizona Medical Center in Phoenix, Arizona, fasting lipid profiles, including TCHOL, high density lipoprotein (HDL), LDL, and TG low density were measured prior to treatment and at the end of treatment (within one month). Testing was performed *via* commercially available assays with Laboratory Corporation of America (Phoenix, Arizona) and Sonora Quest Laboratories (Tempe, Arizona). Metabolic variables were measured at two different time points: (1) prior to treatment (start); and (2) completion of treatment regimen (end of treatment response-ETR).

### Response to treatment

End of treatment response and SVR12 were biochemically defined by an undetectable or below the lower limit of quantification HCV RNA PCR quantitative assay (Laboratory Corporation of America, Phoenix, Arizona and Sonora Quest Laboratories, Tempe, Arizona). Liver enzyme and function tests (including ALT, total bilirubin, and albumin) as well as the protime/INR were recorded before and after treatment using standardized assays at these same laboratories.

### Statistical analysis

Baseline demographics by genotype were compared using descriptive statistics including chi square analysis for categorical variables and one-way ANOVA for continuous variables. Patients not achieving SVR12 were excluded. Changes in lipid profile and liver function tests were evaluated for significance with Levene's test of equal variances and the paired *t* test.

Mean differences were calculated for each component of the lipid profile within each genotype from treatment start to end. Mean differences were compared among genotypes for differences in direction/magnitude by total population and patients with cirrhosis

and non-cirrhosis independently using ANOVA. When significant differences were present, post-hoc analysis was performed using the Bonferroni correction (when equal variances assumed) or Dunnett T3 (when equal variances not assumed) to determine the significantly different pairs. Significance was set at  $P < 0.05$ . Subgroup analysis of the changes in lipid profiles was performed separately for cirrhotics and non-cirrhotics by genotypes.

SPSS software (Statistical Product and Services Solutions, version 22, Chicago, IL, United States) was used for statistical analyses. All authors had access to the study data and had reviewed and approved the final manuscript.

## RESULTS

### Study population

A total of 375 patients were enrolled, of which 321 (85.6%) achieved SVR12 and were included in the study. Of these, 232 (72.3%) had G1, 58 (18.1%) had G2, and 31 (9.7%) had G3. Baseline demographics (Table 1) were similar, including prevalence of diabetes, hypertension, and hyperlipidemia. Incidence of cirrhosis was significantly higher in the G2 group (56.9%) than the G3 group (45.2%). During DAA therapy, serum albumin increased and ALT decreased across all genotypes (all  $P < 0.01$ ). Serum INR improved only in G2 ( $P < 0.001$ ) (Table 2).

### Changes in peripheral lipid profiles during DAA therapy stratified by cirrhosis

On analysis by genotype, significant changes in lipid profiles were seen with GT1 and GT3. In GT1, TCHOL increased from 156.9 to 162.2 mg/dL ( $P = 0.005$ ), LDL increased from 80.2 to 87.6 mg/dL ( $P = 0.058$ ), HDL increased from 51.6 to 63.6 mg/dL ( $P < 0.001$ ), and TG decreased from 114.6 to 108.7 mg/dL ( $P = 0.044$ ). In GT3, TCHOL increased from 141.5 to 157.6 mg/dL ( $P < 0.001$ ), HDL increased 45.4 to 53.3 mg/dL ( $P = 0.038$ ) and LDL increased from 81.4 to 93.9 mg/dL ( $P < 0.001$ ). No significant changes were seen for GT2. These trends were consistent irrespective of the presence or absence of cirrhosis (Table 3). In the total population, absolute pre-treatment TCHOL was lowest in GT3 ( $P = 0.032$ ), however similar between all three groups at the end of treatment ( $P = 0.81$ ).

### Differential effects in peripheral lipid profile based on genotype

On post-hoc comparison of the mean differences in lipid profiles between genotype (GT1 vs GT2 vs GT3, *p*), significant changes were seen in the total population with TCHOL (+5.3 mg/dL vs +0.1 mg/dL vs +16.7 mg/dL,  $P = 0.017$ ) and HDL (+12.3 mg/dL vs +2 mg/dL vs +7.9 mg/dL,  $P = 0.049$ ) (Table 4). GT3 was associated with a greater increase in TCHOL than both GT1 ( $P = 0.028$ ) and GT2 ( $P = 0.019$ ). There was no significant difference in HDL changes between paired

**Table 1** Baseline demographics *n* (%)

	All	Genotype 1	Genotype 2	Genotype 3	<i>P</i> value
Number of patients	321 (100)	232 (72.3)	58 (18.1)	31 (9.7)	
Age (yr)	57.7 ± 10.3	58.9 ± 9.5	55.5 ± 12.1	54.6 ± 10.8	0.009
Gender (male)	221 (68.8)	160 (59.4)	41 (61.2)	20 (64.5)	0.845
Ethnicity					
Caucasian	229 (71.3)	171 (73.7)	40 (70.0)	18 (58.1)	0.018
African American	19 (5.9)	18 (7.8)	1 (1.7)	0 (0.0)	
Hispanic	55 (17.1)	32 (13.8)	13 (22.4)	10 (32.3)	
Asian	16 (5.0)	9 (3.9)	4 (6.9)	3 (9.7)	
Other	2 (0.6)	2 (0.9)	0 (0.0)	0 (0.0)	
Diabetes	79 (24.6)	59 (25.4)	14 (24.2)	6 (19.4)	0.593
Hypertension	132 (41.1)	105 (45.3)	22 (37.9)	5 (16.1)	0.086
Hyperlipidemia	59 (18.4)	44 (19.0)	12 (20.7)	3 (9.7)	0.453
Cirrhotic	150 (46.7)	103 (44.4)	33 (56.9)	14 (45.2)	< 0.001
Treatment					
IFN + SOF + RBV		25 (10.8)	0 (0.0)	0 (0.0)	
SOF + RBV		57 (24.6)	58 (100)	31 (100)	
SOF + SMV		42 (19.0)	0 (0.0)	0 (0.0)	
SOF + LDV		140 (60.3)	0 (0.0)	0 (0.0)	

IFN: Pegylated interferon; SOF: Sofosbuvir; RBV: Ribavirin; SMV: Simeprevir; LDV: Ledipasvir.

**Table 2** Changes in liver function tests

	Genotype 1			Genotype 2			Genotype 3		
	Start Tx	End Tx	<i>P</i> value	Start Tx	End Tx	<i>P</i> value	Start Tx	End Tx	<i>P</i> value
Albumin (g/dL)	3.5 ± 0.6	3.8 ± 0.6	< 0.001	3.5 ± 0.5	3.7 ± 0.6	< 0.002	3.4 ± 0.5	3.7 ± 0.6	< 0.001
ALT (U/L)	70.2 ± 58.3	31.7 ± 38.7	< 0.001	68.7 ± 48.3	26.4 ± 17.8	< 0.001	101.9 ± 61.6	30.7 ± 30.3	< 0.001
Total Bilirubin (mg/dL)	1.0 ± 0.8	0.9 ± 0.8	0.008	1.0 ± 0.9	0.9 ± 0.9	0.202	1.1 ± 0.7	1.1 ± 0.8	0.904
INR	1.1 ± 0.2	1.1 ± 0.3	0.112	1.1 ± 0.1	1.0 ± 0.1	< 0.001	1.1 ± 0.2	1.1 ± 0.3	0.509

ALT: Alanine transaminase; INR: International Normalized Ratio.

**Table 3** Changes in lipid profile by genotype in patients with cirrhosis and non cirrhosis

	Total population			Non-cirrhotics			Cirrhotics		
	Start Tx	End Tx	<i>P</i> value	Start Tx	End Tx	<i>P</i> value	Start Tx	End Tx	<i>P</i> value
Genotype 1									
T Chol	156.9 ± 36.4	162.2 ± 41.0	0.005	169.9 ± 33.2	175.7 ± 38.2	0.046	146.4 ± 35.6	151.4 ± 40.0	0.052
HDL	51.6 ± 18.5	63.9 ± 32.8	< 0.001	54.4 ± 19.5	72.7 ± 36.4	< 0.001	49.3 ± 17.2	56.9 ± 27.6	0.002
LDL	80.2 ± 28.8	87.6 ± 62.7	0.058	87.1 ± 28.1	91.8 ± 31.6	0.091	74.6 ± 28.2	84.2 ± 79.1	0.15
TG	114.6 ± 56.0	108.7 ± 56.0	0.044	117.3 ± 55.1	111.6 ± 57.6	0.27	112.5 ± 56.6	106.4 ± 56.5	0.070
Genotype 2									
T Chol	162.9 ± 35.8	163.0 ± 32.9	0.99	174.2 ± 29.8	173.7 ± 27.5	0.91	148.2 ± 37.7	148.9 ± 34.1	0.90
HDL	52.8 ± 18.6	54.8 ± 20.0	0.39	54.9 ± 17.4	55.3 ± 17.4	0.88	50.0 ± 19.7	54.0 ± 23.0	0.28
LDL	86.7 ± 34.0	87.4 ± 30.2	0.82	95.3 ± 31.8	96.4 ± 27.0	0.82	75.4 ± 33.4	75.7 ± 30.0	0.93
TG	114.3 ± 64.1	112.4 ± 65.8	0.73	120.6 ± 68.4	124.0 ± 74.2	0.72	106.1 ± 59.7	97.1 ± 48.6	0.078
Genotype 3									
T Chol	141.5 ± 38.4	157.6 ± 34.4	< 0.001	161.4 ± 35.5	181.5 ± 23.5	0.001	125.1 ± 32.5	137.9 ± 29.1	0.025
HDL	45.4 ± 15.1	53.3 ± 16.6	0.038	49.3 ± 14.0	53.2 ± 14.3	0.37	42.2 ± 15.3	53.3 ± 18.2	0.065
LDL	81.4 ± 32.1	93.9 ± 34.9	< 0.001	92.5 ± 26.1	110.4 ± 21.4	0.003	72.2 ± 33.6	80.3 ± 37.9	0.045
TG	108.6 ± 47.5	98.8 ± 41.2	0.047	119.0 ± 58.6	112.6 ± 47.1	0.36	100.1 ± 33.4	87.5 ± 31.2	0.12

All values expressed as mean ± SD. All units are in mg/dL. T Chol: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides; Start Tx: Prior to treatment; End Tx: End of treatment.

genotypes on post-hoc analysis. In non-cirrhotics, the trends were similar, with changes in TCHOL (+5.8 mg/dL vs -0.4 mg/dL vs +12.8 mg/dL, *P* = 0.066) and in HDL (+18.2 mg/dL vs +0.5 mg/dL vs +11.1 mg/dL, *P* = 0.008). GT3 was associated with a greater increase in TCHOL than GT2 (*P* = 0.048). Additionally, GT1 was associated with a greater increase in HDL than GT2 (*P*

= 0.012). In cirrhotics, there were no differences seen in the changes in lipid profiles between genotype (Table 4).

## DISCUSSION

Chronic hepatitis C infection is closely linked to lipid metabolism *via* shared use of the classical secretory



**Table 4** Differential effect in lipid profile by genotype in patients with cirrhosis and non-cirrhosis

	All patients				Non-cirrhotics				Cirrhotics			
	GT1	GT2	GT3	P value	GT1	GT2	GT3	P value	GT1	GT2	GT3	P value
T Chol	5.3	0.1	16.1	0.017	5.8	-0.4	12.8	0.066	5.0	0.7	20.1	0.39
HDL	12.3	2.0	7.9	0.049	18.2	0.5	11.1	0.008	7.6	4.0	4.0	0.69
LDL	-5.9	-1.1	-11.9	0.550	4.6	1.0	8.1	0.150	9.7	0.3	17.9	0.82
TG	7.4	2.1	21.2	0.130	-5.7	3.4	-12.6	0.650	-6.1	-9.0	-6.4	0.76

All values expressed as mean  $\pm$  SD. All units are in mg/dL. T Chol: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides; Start Tx: Prior to treatment; End Tx: End of treatment.

pathway<sup>[2,6-8]</sup>; however, specific viral/host protein interactions require further elucidation<sup>[9]</sup>. The link between lipid metabolism and HCV was of particular interest during the era of interferon-based treatment, when components of the metabolic syndrome were identified as negative predictors of achieving SVR<sup>[10]</sup>. However, medications aimed to optimize metabolic syndrome conditions prior to antiviral treatment, such as the PPAR- $\gamma$  agonist pioglitazone and the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor fluvastatin, yielded no significant improvement in SVR rates with pegylated-interferon based therapy<sup>[11-15]</sup>.

Increase in serum cholesterol levels during HCV infection has been demonstrated with successful HCV treatment. Previously identified changes in peripheral lipid profiles included increases in TCHOL and LDL<sup>[4,16-18]</sup>. It has also been associated with increases in HDL<sup>[16,19]</sup>, though not in all studies<sup>[4,17]</sup>. In our study, we found that treatment with DAA resulted in increases in TCHOL, LDL, HDL as well as a decrease in TGs in GT1, and increases in TCHOL, HDL, and LDL in GT3. Changes occurred irrespective of established pre-treatment cirrhosis. GT2 did not have any significant changes in lipid particle concentration. Meissner *et al*<sup>[5]</sup>, in his 2015 study of 55 GT1 patients treated sofosbuvir and ribavirin without interferon, also reported an increase in LDL and decrease in TG, however did not find any significant changes in TCHOL or HDL.

Research on the differences in lipid metabolism between genotypes of hepatitis C have focused mainly on steatosis. A review of 14 studies from 1997 through 2004 estimated the prevalence of steatosis in patients with chronic HCV to be 40%-86% (mean approximately 55%), compared to a baseline of approximately 20%-30% of patients in the United States and other western countries without the virus<sup>[20]</sup>. GT3 in particular is associated with an increased incidence and severity of hepatic steatosis, estimated at 73% in this same study<sup>[20]</sup>. This steatosis, in contrast to GT1, is independent of any co-existing insulin resistance or obesity<sup>[1-3]</sup>. Hypcholesterolemia has been found to various extents across genotypes and is also known to be more pronounced in patients with GT3<sup>[21,22]</sup>. This was also seen in our study. While the exact mechanism is unknown, it likely relates to alterations of the distal cholesterol synthesis pathway<sup>[23]</sup>.

Relatively little is known about the different effect of genotypes on the magnitude of lipid profile changes

from start to end of treatment. One study identified that only GT3 treatment responders, but not non-responders or any GT1 patients, demonstrate an increase in serum cholesterol<sup>[24]</sup>. A more recent investigation found significant post-therapeutic increases in TCHOL, LDL, HDL, and TGs, but greater increases in HDL in patients with GT2<sup>[16]</sup>. All of the aforementioned analyses primarily included subjects treated with interferon and ribavirin.

Our study is the first to compare mean differences in lipid profile components between GT1, GT2, and GT3 after treatment with DAAs. We found patients with GT3 to have the most profound changes in lipid profile, characterized by a significantly greater increase in TCHOL than both GT1 and GT2 across the entire population. This was also reflected in our cirrhotic and non-cirrhotic subgroups. On the other hand, the lipid profiles of patient with GT2 were relatively unaffected by treatment in the cirrhotics, non-cirrhotics, and combined analysis, though the reason for this is unclear. Nonetheless, GT2 experienced improvement in synthetic function congruent with GT1 and GT3, as noted by an increase in albumin, and perhaps even better than GT1 and GT3 as evidenced by the significant improvement in INR not seen in the other two genotypes.

Unfavorable lipid changes are most pronounced in those with HCV GT3 infection who are successfully treated with DAAs. This may be a reflection of the more severe hypocholesterolemia that affects this group prior to treatment. Here, the increase in TCHOL brought it into a range that was not significantly different than either GT1 or GT2. The long term effect of the change in lipid profiles on cardiovascular risk and mortality is unknown, though it has been demonstrated that that patients successfully treated for HCV have lipid profiles may return to levels that potentially increase coronary disease risk<sup>[4]</sup>. Long term follow-up of these patients is warranted to correlate these changes with clinical outcomes.

## COMMENTS

### Background

Different genotypes of the hepatitis C virus (HCV) are associated with differing levels of hepatic steatosis, with genotype 3 having the strongest direct association.

## Innovations and breakthroughs

In this investigation, change in peripheral lipid panels during direct-acting antiviral therapy were assessed in a large HCV treatment cohort with respect to genotype. Total cholesterol in patients with genotype 3 increased significantly during treatment compared to other genotypes. Associated steatosis and differing lipid kinetics may influence response rates to direct acting therapy and may also influence genotype specific risks of hepatic and systemic complications.

## Peer-review

The authors deal with a very interesting topic concerning the genotype specific peripheral lipid changes during daa therapy are uncharacterized. The manuscript is well written and although only four markers are used to support the scientific hypothesis data are promising.

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