

# Analysis of the lipidome in chronic hepatitis C shows genotypic differences which resolve with viral clearance

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## INTRODUCTION

HCV genotype (G) 3 has been associated with more hepatic steatosis, accelerated fibrogenesis and an increased risk of hepatocellular cancer (HCC), compared to G1<sup>1,2</sup>. We hypothesized that this may be due, in part, to virally-mediated differences in lipid metabolism.

## METHODS

We compared the serum lipidome between subjects infected with HCV G1 and G3, both in the fasting [G1 n= 71, G3 n = 39] and non-fasting states (G1 n = 75, G3 n =75) and after sustained virological response (SVR) (G1 n=50, G3 n = 50).

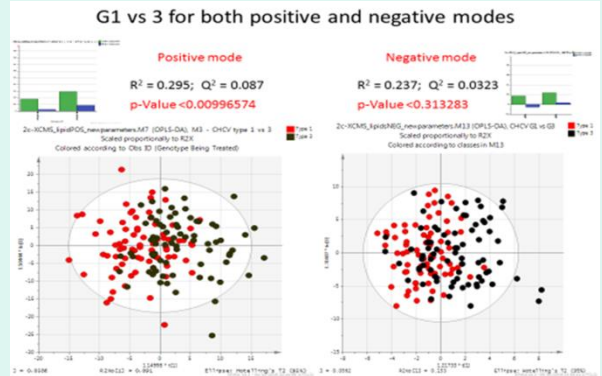
We performed serum lipid UPLC-MS profiling using an ACQUITY UPLC system coupled to a Q-ToF Premier mass spectrometer using an electrospray (ESI) ion source operated in both positive and negative electrospray ionization modes (ESI+ and ESI-).

## RESULTS

The UPLC-MS spectra from sera were explored by principle component analysis (PCA) to detect clusters and outliers. In chronic HCV (CHCV), the sera of the fasting subjects showed the strongest genotypic separation

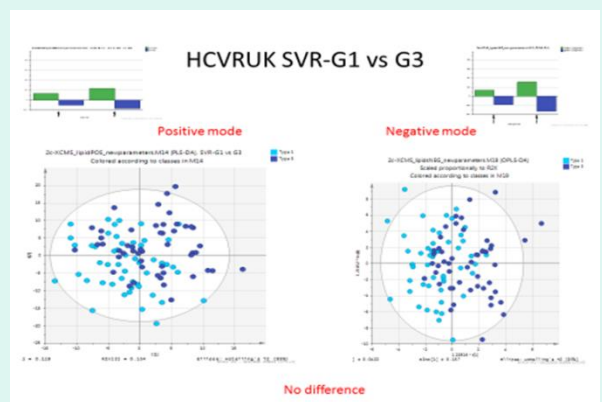
## RESULTS (cont.)

Figure 3: Principal components analysis (PCA) of *non-fasting* sera, (HCV Research UK cohort: RNA positive, viraemic) in both positive and negative electrospray ionisation mode.



In order to determine whether lipidomic differences resolve or persist after successful eradication of HCV following SVR, further analysis was performed on a third cohort of non-viraemic post SVR samples. PCA demonstrates that there is no significant separation by previous HCV genotype exposure following SVR

Figure 4: PCA of *non-fasting* sera, (HCV RNA negative, non-viraemic) following SVR to pegylated interferon-alpha and ribavirin in both positive and negative electrospray ionisation mode.



## CONCLUSIONS

This study supports the notion that the observed genotype-specific alterations in the lipid metabolism in chronic HCV infection are due to the presence of active HCV replication and resolve with viral clearance.

Lipidomics analysis reveals lipid species associated with reverse cholesterol transport specifically increased in HCV-G3, which may have important clinical implications for liver disease progression and promotion of HCC, a leading cause of cancer death world-wide, via lipid synthesis<sup>3</sup>.

## REFERENCES:

1. Rubbia-Brandt L et al. *Gut*, 2004 Mar;53(3):406-12.
2. Leonardo A et al. *World J Gastroenterol*, 2014 Jun 21;20(23):7089-103
3. Gury Y et al. *Cancer Cell*, 2017 Dec 11;32(6):807-823

Figure 1: Principal component analysis (PCA) of *fasting* CHCV sera in positive electrospray ionisation mode demonstrating separation between HCV genotypes.

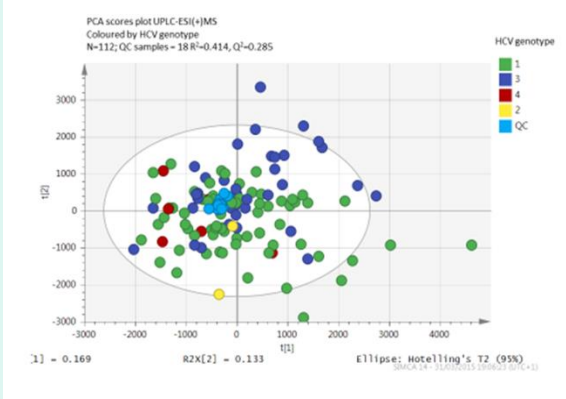
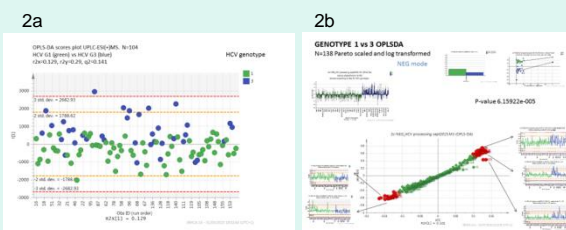


Figure 2: OPLS-DA scores plot to identify those variables with greatest influence to separation of HCV genotypes 1 & 3 in a) electrospray ionisation (ESI) positive & b) ESI negative mode.



Preliminary assignment based on mass, fragmentation pattern and retention time identified lipid species upregulated in HCV-G3 including *Cholesteryl linoleate*.

Additional novel lipid species were found to be differentially upregulated in HCV-G1 in the analysis in the negative ion mode. Assignment of lipid species identified phosphocholines: e.g. PC (36:3) increased in HCV-G1, whereas cholesterol esters were the discriminant features increased in HCV-G3