Profiling lipid metabolism alterations in genetic FTD within the GENFI cohort

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Background

Although frontotemporal dementia (FTD) is a heterogeneous disease, lysosomal dysfunction and inflammation appear to be affected across all forms causing alterations on lipid metabolism. With the lack of fluid biomarkers specific for FTD we explored alterations in lipid metabolism in serum samples from the GENFI cohort.

Methods

A total of 522 serum samples from GENFI were analysed using the Nightingale Blood Biomarker Analysis Service (Nightingale Health Ltd.). In this cross-sectional study we included 113 symptomatic FTD mutation carriers, 205 presymptomatic mutation carriers and 204 non-carrier family members (Figure 1). In total, 220 metabolites were analysed using a NMR based metabolomics technology. Bootstrapped regression analysis was performed to compare groups adjusting for age and sex.

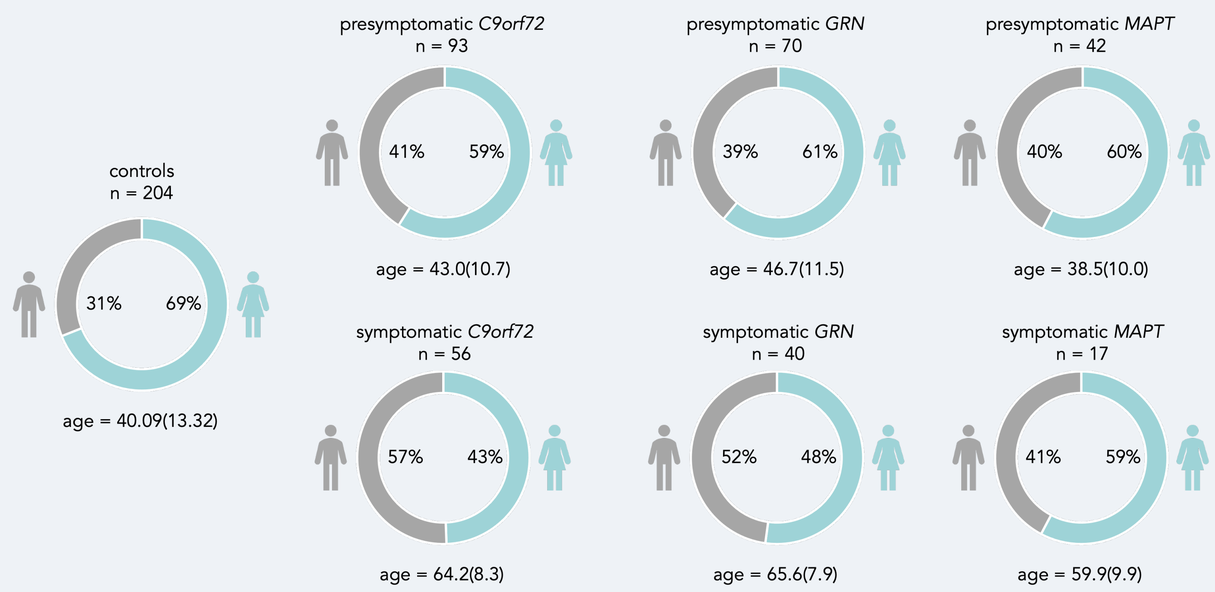

Figure 1. Participant demographics. Age indicated as mean(sd).

Results

Volcano plots with pairwise comparisons of the symptomatic groups with controls were generated from the measures of 69 of the 220 metabolites (Figure 2). The pattern of metabolites altered in each genetic group when compared to controls was different with a decrease in pyruvate in symptomatic *C9orf72* expansion carriers, an increase in total HDL particle concentration in symptomatic *GRN* and a decrease in creatinine in symptomatic *MAPT* mutation carriers as the most significant changes. The total concentration of lipoprotein particles and apolipoprotein A1 were significantly increased in all symptomatic groups. We also visualised the pattern of changes between controls and presymptomatic mutation carriers with only presymptomatic *MAPT* mutation carriers showing significant differences.

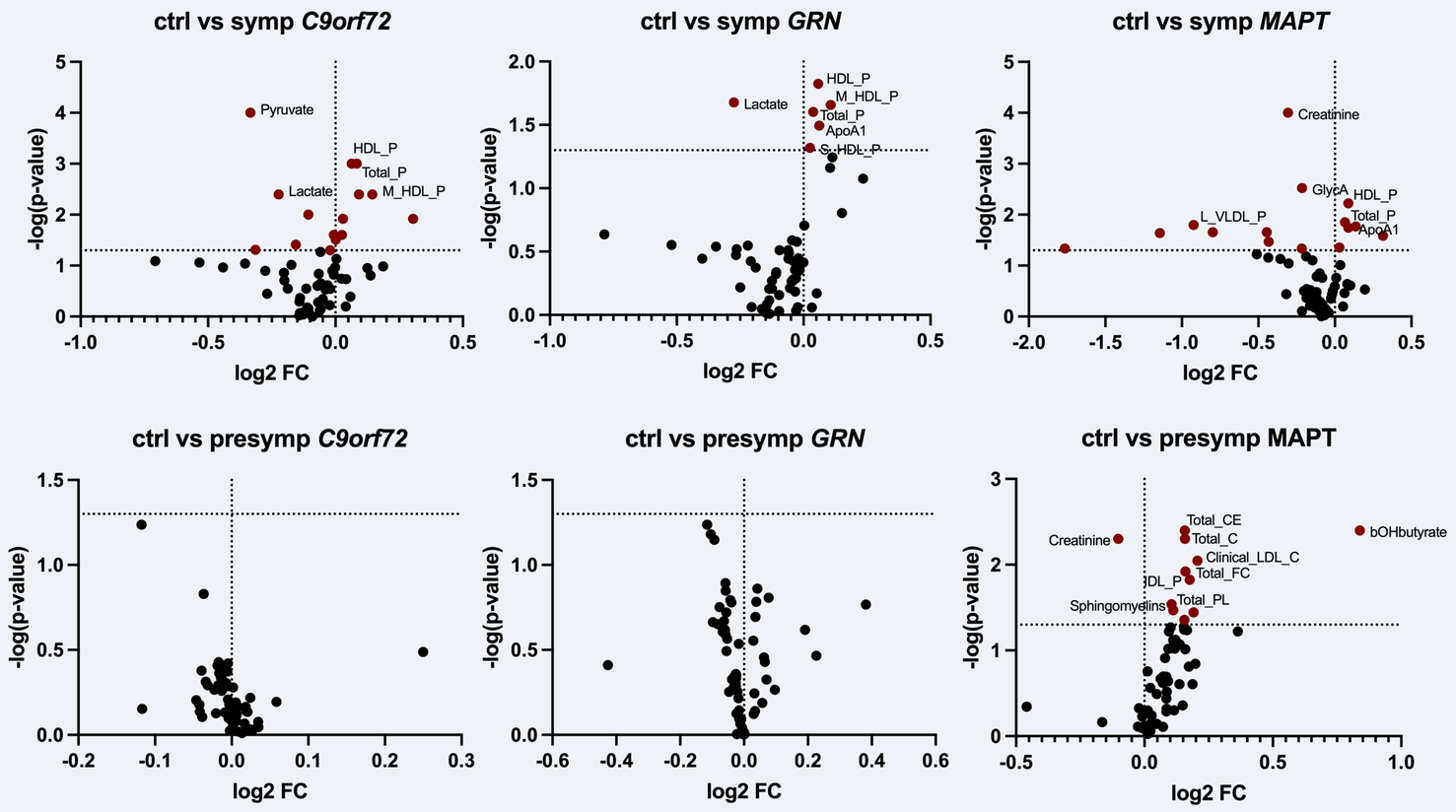

Figure 2. Volcano plots generated from the negative logarithm of the p-value from linear regression with pairwise comparison and the logarithm in base 2 of the fold change.

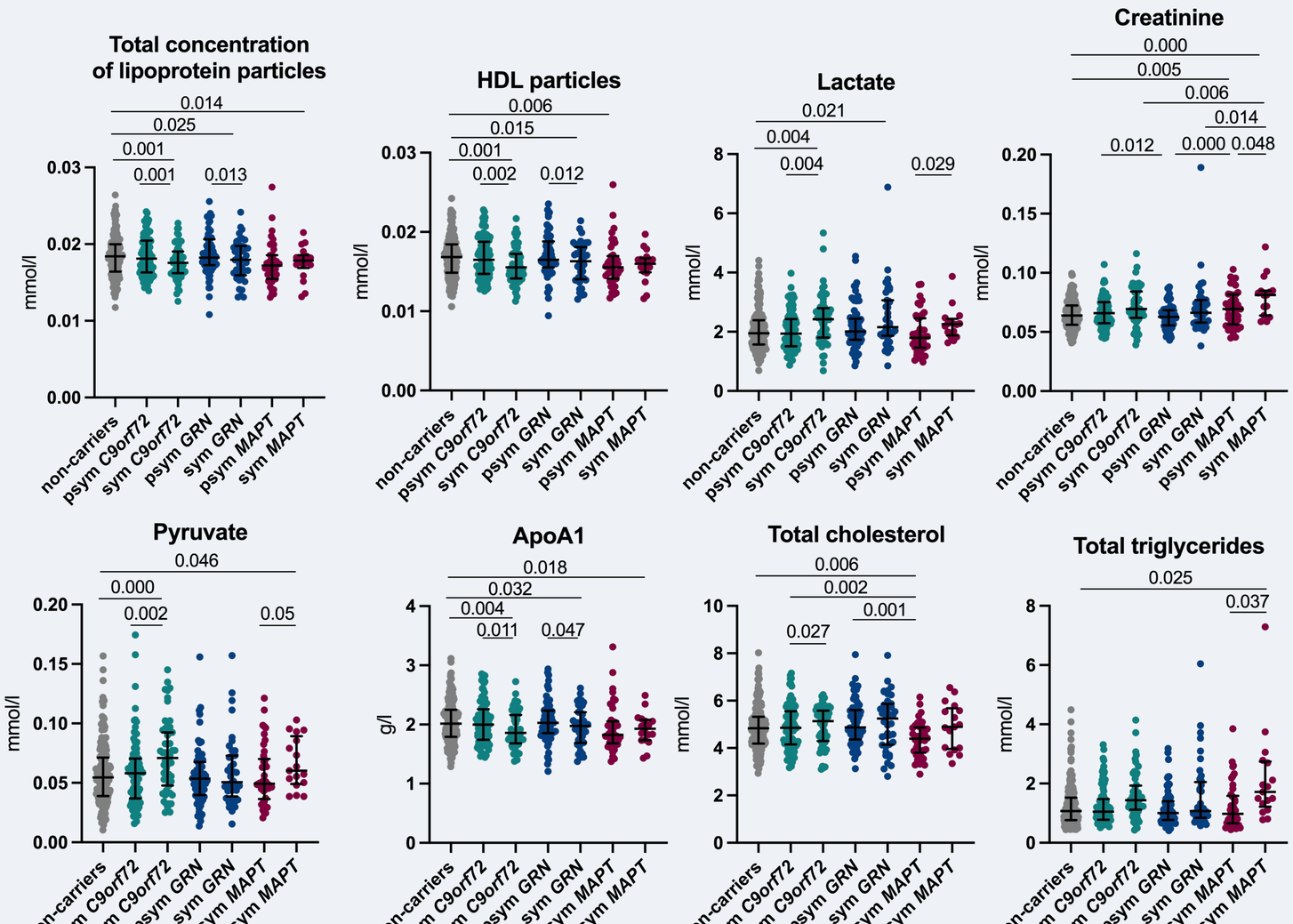

Figure 3. Levels of the top metabolite hits in the study. Units shown in the x axis. p-values of linear regression followed by pairwise comparison indicated in the graph.

The top metabolites identified in the volcano plots were analysed separately in all clinical groups (Figure 3). Total concentration of lipoprotein particles is in general decreased in the symptomatic groups, as well as the HDL particles count and apolipoprotein A1. In contrast, the levels of lactate, creatinine and pyruvate were generally increased in symptomatic groups. Similarly, the total cholesterol levels were increased in symptomatic *C9orf72* and *GRN* carriers, whilst total triglycerides were increased only in the symptomatic *MAPT* group.

Conclusion

The present study shows alterations in the metabolome in the genetic forms of FTD, specifically in the symptomatic groups when compared to controls. In the case of *MAPT* mutation carriers, the changes in metabolites start already at the presymptomatic stage. These results indicate the complexity in metabolic changes associated with each genetic group. Further cluster analyses may identify patterns of alterations that could suggest specific underlying disease mechanisms.

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