Utility of Metabolomics Screening in Familial Hypercholesterolemia in Combination with Genetic Diagnosis

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Familial hypercholesterolemia (FH) is one of the most common congenital metabolic disorders predisposing to premature cardiovascular disease (CVD). Recent studies have shown that the condition is more complex than previously thought, with multiple causal genes and largely unknown effects on lipoprotein metabolism. In the past studies, lipid measurements have however been usually limited to total cholesterol, HDL and LDL despite the existence of continuum of lipoprotein particles.

METHODS

We have developed a high-throughput metabolomics platform for population-wide initiatives and screening programs. Given its throughput and cost-efficiency, it has become the standard in the world's largest health initiatives and is, e.g., being applied to profile the entire collection of UK Biobank with 500,000 samples. With 61 quantified measures of lipoprotein particle concentrations and their associated lipids categorized by particle size, our platform is especially suited for enhanced screening of lipid conditions.

STUDY DESIGN

FH N=13, CONTROLS N=14

NMR METABOLOMICS
229 metabolic measures

ASSOCIATIONS BETWEEN METABOLITES & FH

RESULTS

Metabolomic profiling of FH patients and high LDL controls reveals a metabolomic signature that is specific for underlying FH. The FH signature includes increases in all apoB carrying lipoprotein subclasses, which have been suggested to have a causal role in CVD, independent of LDL cholesterol. The results show that comprehensive metabolomic profiling can be useful in discriminating FH from lifestyle-induced dyslipidemias or polygenic forms of hypercholesterolemia. However, LDL levels alone are inadequate to capture the metabolomic signature of FH.

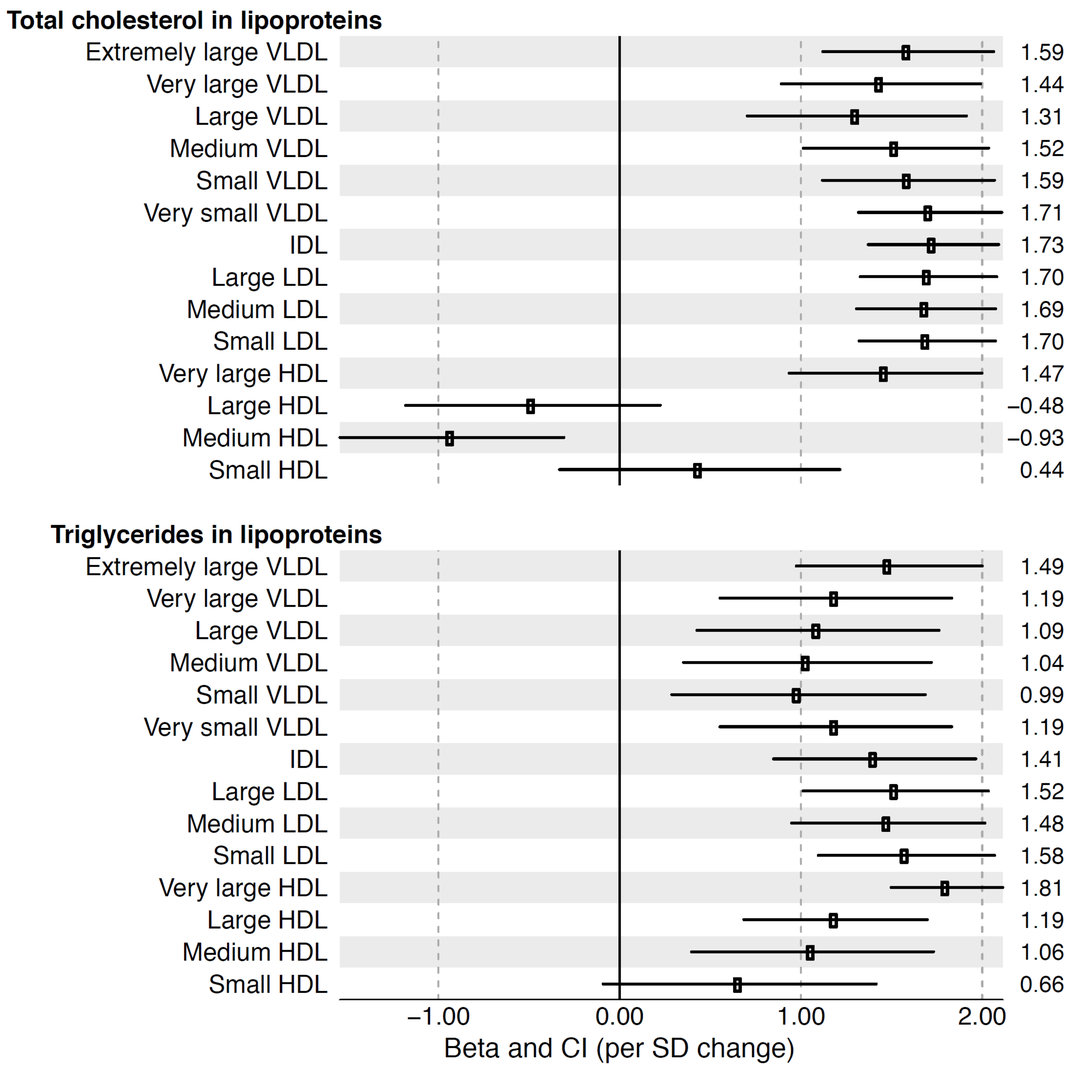

Figure: Metabolomic profiling of patients with FH and LDL controls reveals a metabolomic signature that is specific for FH.

CONCLUSIONS

Population-wide high-throughput metabolomic screening combined with molecular analysis by an FH NGS panel (including the genes APOB, LDLR & PCSK9) could help identify FH patients more accurately than LDL screening alone. We believe that this approach can provide a better understanding of the molecular effects of FH, discriminate from polygenic forms of the disease and other dyslipidemias, leading to prevention of premature heart disease and facilitate precision medicine style treatment modality.

REFERENCES

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