Unlocking the Power of Multiomics

Multiomics approaches are on their way to revolutionize medicine and biology. Being major players in cardiovascular disease research, genomics and lipidomics are perfectly suited for a joint multiomics approach. Combining genomic risk prediction with lipidomic phenotyping will result in an effective payoff. This white paper will answer how linking the lipid phenotype to the genotype will improve performance and showcase immediate and future consequences for prevention, clinical diagnostics and drug research.

genomics | lipidomics | SNP-based heritability | disease risk factors | prevention

The Future is Multiomics

With an ever-increasing pool of accessible information and new tools to mine huge data sets, biology and medicine are moving from intervention to prevention. Omics sciences like genomics and lipidomics will be strong contributors to this paradigm shift. However, looking at data from only one omics approach limits explanatory power. Multiomics approaches with data sets from more than one omics discipline are the weapon of choice. They strengthen synergies and eliminate shortcomings to effectively deliver what one omics science alone cannot achieve. Linking genotype with phenotype will be critical when it comes to clinical diagnostics and to the goal of identifying the onsets of a disease.

The compelling reason for combining omics sciences, is that this provides a more conclusive picture. The genotype portrays the given settings, the phenotype measures the present state. This is why combining genomics with lipidomics makes for a great multiomics pair. It matches the capacity to identify genetic predestinations with one or multiple snapshots of the lipid metabolic status.

Genomics for Genes

Where genetics zeroes in on the composition and functioning of one gene, genomics addresses the sum of all genes, the genome, and their interrelationships. The system biology of genes delivers genome mapping and editing data, illuminates structure and function relationships and gives insights into evolutionary processes. The most important outcome is the DNA sequence. Genomics is the 'oldest' omics science and sounded the bell for the age of systems biology.

One of the most fascinating applications of genomics is determining clinical disease risk factors. After all, the genome will mainly stay unchanged and so will its genetic predispositions. Researchers have been dreaming of a full genome sequence that once in a life time will give information of how a patient should live her/his life. But although many spots in the genome have been linked to an increased risk for cardiovascular disease, this dream has come to an end. Because a genetic setting simply speaking only regulates how genes are actively transcribed and translated into proteins, the influence is limited. These proteins then regulate the organism's metabolism and ultimately also behaviour but many environmental factors come into play as well. Neither does genomic data give insight into how much a gene manifests itself in a phenotype nor whether it is active at all. The consequence: genomic data alone can only determine risk scores with low predictive power. This is not sufficient to make a patient change her/his lifestyle. However, there is a tool with great capacity to predict future cardiovascular disease events based on current readouts. This tool is lipidomics.

Lipidomics for Lipids

In analogy to genomics, lipidomics is the study of lipids and lipid metabolites in biological systems. Targeting thousands of chemically distinct lipid molecules, lipidomics unveils the many different biological functions of lipids which range from storing energy, serving as hormones and signalling molecules to forming the cell membrane. Like sequencing DNA in genomics, the omics of lipids has developed technology to analyse the lipid composition in cells and body fluids. Lipidomics used to be considered a subgenre of metabolomics. But due to its rapid increase in popularity and applicability lipidomics acquired independence and today is often quoted as the fastest growing omics science. However, lipids are by no means new to clinical diagnostics.

Levels and changes of blood plasma lipids have been used for decades to monitor and predict risk for cardiovascular diseases. The widely used traditional lipid panel often presents four data points total triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol levels. These are then to be interpreted by a physician. However, human blood plasma comes with hundreds of chemically distinct lipids, a full lipidome. Besides outperforming the explanatory power of traditional lipid panels by far, lipidomics analysis achieves what genomics cannot. It provides detailed insights into the current state of a patient's metabolism, his/her lipid phenotype. Lipidomics unlocks the power to match genetic predestinations with hands-on lipid data and this enhances disease risk predictions. Thus, together they finally accomplish what clinical research has been dreaming of: detailed lifestyle recommendations.

When reviewing what lipidomics adds to genomics, one question should be answered.

Can Lipids Species Levels be Inherited?

Heritability is the part of a trait contributed by the genome. As such, it cannot be explained by environmental factors. Genomics has developed different methods that can deliver genetic information. One example is single-nucleotide polymorphisms (SNPs). SNPs are genetic variations in just one nucleotide. For example, most people may have the genetic code AACGCT at a specific position but some might feature AATGCT instead.

In SNP-based heritability calculation, a large number of SNPs from genomes are drawn and then correlated with corresponding traits such as cardiovascular disease. If a SNP appears in many people who have experienced a cardiovascular disease, the SNP is correlated to the disease. Based on the numbers, a heritability estimate score is calculated. It ranges from 0 (not inherited) to 1 (inherited). However, finding such SNPs in an individual who has not had a cardiovascular disease, does not imply that a stroke or coronary infarct in the future is a certainty. As explained earlier, genomics neither gives insight into how much readout a gene 'produces' nor whether it is active at all.

The concept of SNP-based heritability estimation can also be applied to lipid levels. While this has been done for data from traditional lipid panels, this has not yet been performed for lipidomics data to the extent presented herein. However, that is where it gets interesting.

Lipotype Shotgun Lipidomics for Plasma Samples

Lipotype Shotgun Lipidomics technology utilizes the advantages of cutting-edge mass spectrometry combined with automated sample extraction, processing and data analysis. This technological advancement allows for the analysis of hundreds of samples per day, reducing result delivery time to weeks instead of months. This includes all absolutely quantified individual lipid data and associated reports.

Lipotype Shotgun Lipidomics is an exquisitely standardized technology. It is highly reproducible[1] and routinely covers 30 different lipid classes on the level of lipid species or subspecies – in total more than 2300 individual lipids. The crucial point: while Lipotype Shotgun Lipidomics supports a wide range of sample types it requires only minimal amounts of sample per analysis, e.g. 1μL of blood plasma is sufficient.

Workflow of Lipotype Shotgun Lipidomics

SAMPLE extraction → SAMPLE infusion → MS analysis → LIPID identification → DATA analysis

Genes and their Contribution to the Lipidome

The results of the SNP-based lipid heritability study reveal that there are considerable variations across lipid classes **(Figure 1A)**. Median heritability estimates range from 0.19 for phosphatidyl-inositols (PI) to 0.39 for ceramides (Cer). This means, ceramides are inherited to a stronger degree than phosphatidylinositols. However, when comparing saturation degree and chain length of the fatty acids, a strong pattern emerges **(Figure 1B)**. Lipids containing polyunsaturated fatty acids, particularly chain lengths of 20 carbon atoms with four, five or six double bonds have significantly higher heritability than other lipid species.[2]
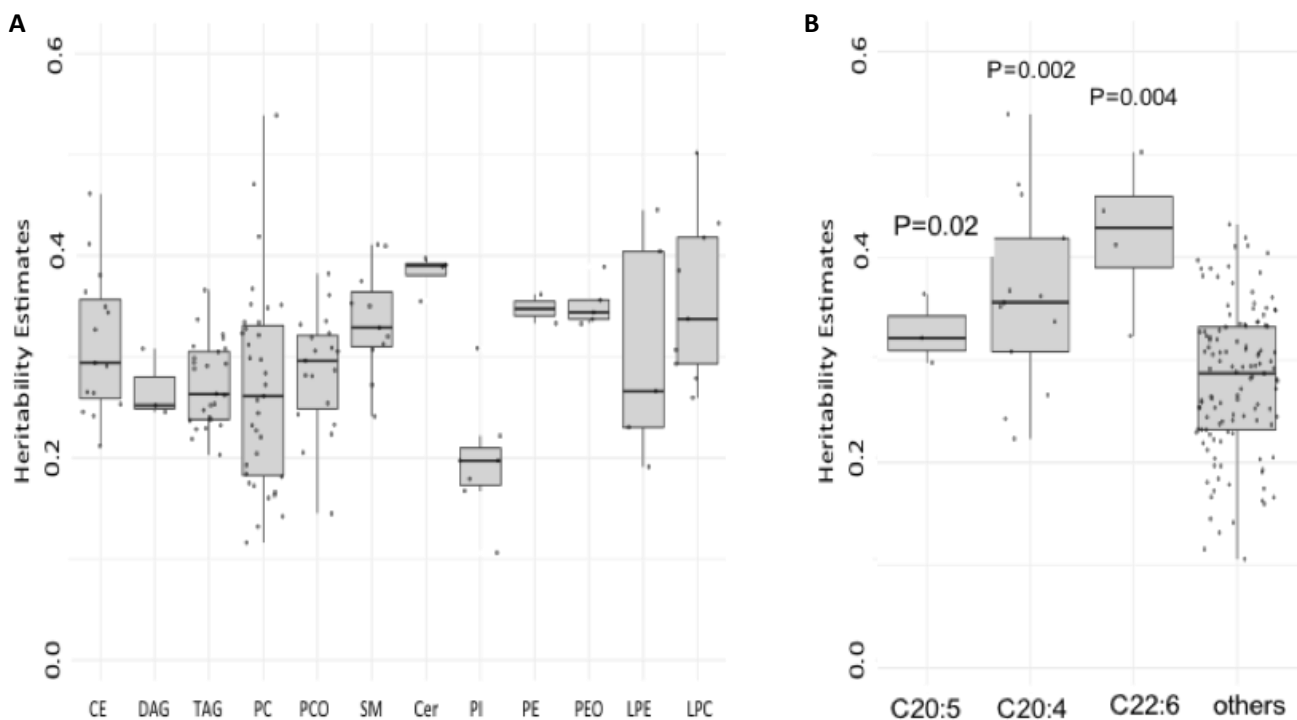
Figure 1: Heritability of lipidomic profiles and genetic correlations among the lipid species. A Median heritability estimates in each lipid class. **B** Heritability estimates based on selected fatty acid chains in lipid species.[2]

This shows that despite dietary influences on the blood plasma lipidome, lipid species levels are inheritable. While a person's lipid metabolism is likely considerably genetically influenced, this does not apply to all lipid species in the same way. Longer, and more saturated lipids feature a stronger genetic sharing. So where does this information take us?

# From Genome to Phenome: Interconnected Disease Risk Factors

WHO warns: cardiovascular diseases have moved to the top spot when it comes to mortality and morbidity globally[3]. With lipids as known disease risk factors for cardiovascular diseases, genetic predispositions influencing the lipidome provide invaluable information, especially for clinical diagnostics. Until today, many of the known genetic regions associated with lipids have no clear relation to cardiovascular disease risk prediction. This has now changed.

Recent data using this multiomics approach led to the identification of a SNP within the gene *BLK (tyrosine kinase of the src family of proto-oncogenes)* associated with decreased risk of obesity and hypertension, and increased risk of gallstones. But this is just one of the many SNPs linked to disease risks, which have been unravelled by combining SNPs with lipidomics.[2]

Nonetheless, the approach is by no means limited to cardiovascular diseases but can be employed for other diseases, too. Combining data from genomics and lipidomics, this study sheds light on lipid biology and corresponding genetic factors associated with disease risks. It provides novel information that might guide devising disease prevention strategies.

One More Thing

At the beginning, it was unclear whether a multiomics approach would provide more in-depth information. Associating genomics data with traditional lipid panel measures might just have done the job. To find out, both approaches have been pursued. By comparing the capacity of traditional lipid panel measures **(Figure 2, upper panel)** and lipidome data **(Figure 2, lower panel)** to discover lipid associated SNPs, it became crystal-clear that molecular lipidomic data have much stronger association (lower P values). It trumps traditional lipid panel measures by several orders of magnitude. Moreover, lipidomics provides greater statistical power to identify SNPs with direct roles in lipid metabolism. This is necessary to capture individual lipids as potent independent disease risk factors. All of which the traditional lipid measures used in clinical routine fail to do.[2]
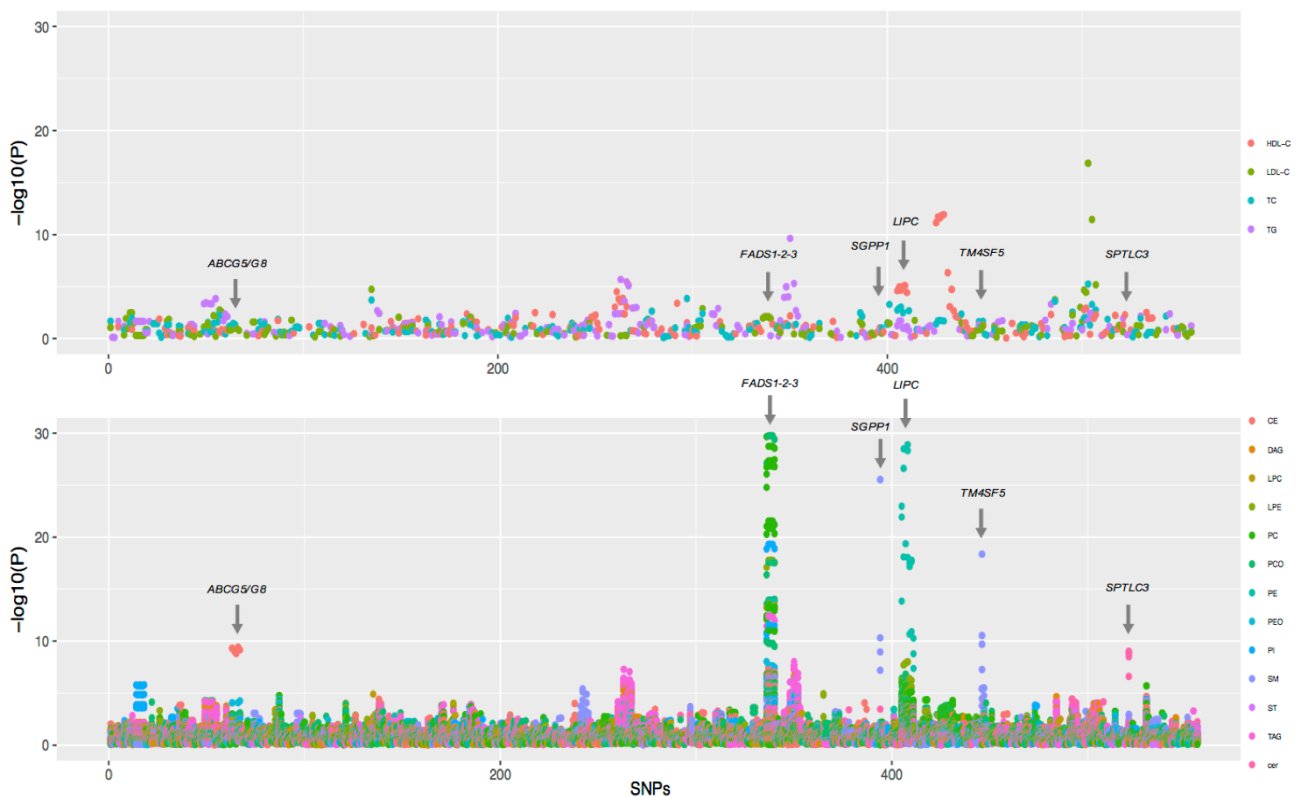
Figure 2: Explanatory power of traditional lipid measurements and lipidomics analysis in comparison. Association of known SNPs for traditional lipids with traditional lipid measurements (upper panel) and lipidomics analysis data (lower panel). Noticeable associations have been annotated.[2]

In conclusion, genomic predispositions profit from lipidomics data and vice versa. It unlocks the power to align genetic risks with phenotypes. By enabling early identification of disease onsets, it helps to maximize prevention performance. Where traditional lipid panel measures fail, lipidomics proves that it has by far the higher potential for clinical diagnostics and research. This power will be enhanced when other omics methods are included. The multiomics power may indeed open doors not only to prevention, lifestyle recommendations and diagnostics but also to new drug targets.

Biology and medicine are now moving from intervention to prevention. Multi-omics will be the fuel required for the take off.

Unlock the Power of Multi-Omics!

Lipotype Shotgun Lipidomics technology and our dedicated team of lipid, bioinformatics and statistics experts provide the fundaments to take your research project to the next level. Employ it for lipid identification and absolute quantification in basic and clinical research, for the biotech, pharma, food and cosmetics industry, for routine clinical diagnostics or personalized healthcare. Lipids are essential to every cell. Make them essential to your research.

Lipotype Shotgun Lipidomics can be employed for multiomics approaches like…

- Genomics-lipidomics studies for drug target discovery
- Genomics-proteomics-lipidomics complex analysis for basic research
- Proteomics-lipidomics skin analysis for novel cosmetics and dermatology
- And many more…

References

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2   Rubina Tabassum et al. "Genetics of human plasma lipidome: Understanding lipid metabolism and its link to diseases beyond traditional lipids" bioRxiv 2018, bioarxiv.com/content/genetics-of-human-plasma-lipidome
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