

NUTRIGENOMICS AND PERSONALIZED NUTRITION: MOLECULAR INSIGHTS INTO METABOLIC HEALTH AND DISEASE PREVENTION

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ABSTRACT

Complex interactions between genetic variation, nutrition, lipid metabolism and environmental exposures play a role in metabolic diseases. While nutrigenomics is growing in significance for precision nutrition studies, systems-level (whole organism) characterization of metabolic nutrigenomic interactions is underdeveloped. This study investigated nutrigenomic associations linked to metabolic health and disease prevention using statistical, network-based, and functional enrichment approaches. A curated dataset containing experimentally validated gene–trait associations was analyzed using computational workflows, including disease categorization, descriptive statistical analysis, hub-gene prioritization, gene–trait interaction network construction, and pathway enrichment analysis. The dataset comprised 144,377 metabolic nutrigenomic records involving 194 genes, 541 SNPs, 392 disease traits, and 3,535 PubMed references. Cardiovascular lipid disorders represented the dominant disease category, followed by liver NAFLD and obesity. Network-centrality analysis identified ZPR1, GCKR, APOE, and PCSK9 as the most interconnected hub genes across metabolic phenotypes. Additional genes, including LPL, APOB, ANGPTL4, TM6SF2, LPA, and LIPG, formed interconnected metabolic modules associated with lipid transport, triglyceride regulation, and hepatic fat metabolism. Functional enrichment analysis demonstrated significant overrepresentation of pathways related to cholesterol homeostasis, triglyceride metabolism, cholesterol metabolism, PPAR signaling, plasma lipoprotein remodeling, chylomicron clearance, and HDL remodeling. These findings indicate that metabolic nutrigenomic associations are predominantly organized around lipid-regulatory biology and lipoprotein dynamics. The results support a systems-level framework for personalized nutrition in which interconnected metabolic pathways and gene networks may contribute to targeted strategies for metabolic disease prevention and nutritional intervention.

KEYWORDS: nutrigenomics, personalized nutrition, metabolic disease, lipid metabolism, functional enrichment

INTRODUCTION

The metabolic diseases are among the most pressing global public health concerns because they continue to be a growing problem, are associated with chronic complications, and are linked to morbidity and mortality. Obesity, dyslipidaemia, nonalcoholic fatty liver disease (NAFLD), insulin resistance and cardiovascular diseases all play a role in significant metabolic dysfunction in populations around the world. Over the last 20 years, there has been an upward trend in the number of people with metabolic diseases globally, supported by epidemiological evidence, which shows that there are significant changes in dietary patterns, sedentary behavior and environmental risk factors (Chew et al., 2023). Obesity is especially a key metabolic pathway that leads to various downstream disorders such as type 2 diabetes, hepatic steatosis, chronic inflammation, and progression of cardiovascular diseases (Yang et al., 2022).

Although the exact mechanisms of metabolic disorders are very complicated and are linked with factors such as genetic susceptibility, lipid metabolism, inflammatory signaling, insulin resistance, and nutritional exposures. It has been shown that dysregulated adipose tissue metabolism and chronic low-grade inflammation are key players linking obesity-related metabolic dysfunctions to the progression of cardiovascular and hepatic diseases (Gutierrez-Cuevas et al., 2021). Genetic susceptibility is also a significant factor in determining individual susceptibility to metabolic diseases, and genome-wide association studies have identified many variants associated with obesity, lipid regulation, glucose metabolism and hepatic fat accumulation (Barroso & McCarthy, 2019). Moreover, insulin resistance is known to play a central role in the pathogenesis of obesity, diabetes,

dyslipidemia, and cardiovascular disease as a result of impaired glucose utilization and lipid homeostasis (Zhao et al., 2023).

As insights into gene–environment interactions have increased, so has the interest in nutrigenomics and nutrigenetics as new scientific areas in precision medicine. While nutrigenomics examines the effect of nutrients on gene expression and metabolic pathways, nutrigenetics shifts the spotlight to how genetic variation affects the response to nutrients and dietary patterns. These methods have become more relevant over the last few years due to their ability to offer personal dietary methods and disease prevention strategies based on genetic profiles (Nasir et al., 2022). Computational biology and integration of genomic data have allowed the generation of large nutrigenomic reference resources, which provide a systematic catalogue of nutrigenomics-related genetic polymorphisms and their disease associations (De Filippis et al., 2025).

The latest research has shown that nutrigenomic regulation is a crucial factor in obesity, insulin resistance and type 2 diabetes, impacting lipid metabolism, inflammatory responses, adipocyte differentiation and glucose homeostasis. The integrative nutrition strategy, which combines functional foods, microbiome modulation, and nutrigenomic profiling, has demonstrated promising potential in enhancing metabolic disease management and tailoring nutrition interventions to individual patients' needs (Lam et al., 2025). Furthermore, dyslipidaemic metabolic pathways are emerging as molecular systems linked to each other, such as intra- and inter-lipid signaling, cholesterol transport and triglycerides regulation, alongside the role of oxidative stress, which all play a role in the progression of cardiometabolic disease (Paduraru et al., 2025).

Multiple genes related to lipid transport and metabolic processing in the liver have been found to play a recurrent role in susceptibility to metabolic diseases. Genes of interest for fatty liver disease and lipid metabolism, such as APOE, PNPLA3 and TM6SF2, have been strongly associated with fatty liver disease and lipid metabolism, highlighting the role of hepatic lipid regulatory mechanisms in metabolic pathology (Jamialahmadi et al., 2021). However, previous studies in humans are mostly directed toward specific genes, pathways or single metabolic disorders, and do not consider the study of network structure of molecular interactions for multiple disease phenotypes.

The growing amount of large-scale genomic data has made systems biology and network-based analytical approaches for understanding complex disease mechanisms more important. Conventional association studies may fail to identify highly connected hub genes, interaction modules, and biologically enriched pathways, which can be successfully identified using functional genomics and network biology approaches (Joshi et al., 2024). Network-based approaches have also been shown to be highly useful in characterizing molecular interactions within complex diseases by discovering interconnected biological modules and disease-relevant pathways (Choobdar et al., 2019). These may be relevant, especially in the field of nutrigenomics, where metabolic diseases are controlled by tightly interconnected metabolic pathways, including lipid transport, energy metabolism, inflammatory signaling, and nutrient-responsive genes.

While there is previous work that has described the significance of nutrigenomic interactions in metabolic diseases, there are still some significant limitations. Current research often focuses on individual disease classes or individual gene studies and doesn't incorporate many metabolic phenotypes in a systems-level approach. Furthermore, only a few studies have integrated large nutrigenomic data sets with functional enrichment and network centrality methods for the purpose of identifying key molecular factors associated with metabolic diseases. The role of comprehensive evaluation of hub genes, semantic relationships, and pathway-level interactions in obesity, cardiovascular lipid disorders, NAFLD and diabetes is still not sufficiently explored.

Thus, the present study was undertaken to explore nutrigenomic associations related to metabolic diseases by a combination of bioinformatics and a network-based analytical approach. The study aimed at the identification of major hub genes, the identification of disease-specific nutrigenomic distributions, the construction of gene–trait interaction networks and the evaluation of biological pathway enrichment involving metabolic nutrigenomic regulation. This study aimed to gain a systems-level understanding of the molecular mechanisms underlying metabolic health and disease prevention using a combination of statistical analysis, network biology and functional enrichment approaches, within the context of personalized nutrition.

2. METHODOLOGY

2.1 Research Design

In this study, a computational bioinformatics and network-based analytical design approach was used to explore nutrigenomic associations with metabolic disorders. A secondary data analysis approach was used in a retrospective manner to determine major gene–trait interactions, to understand disease-specific nutrigenomic patterns, and to assess the biological pathways associated with highly connected hub genes. The methodology adopted involves data preprocessing, descriptive statistical analysis, network construction, hub-gene prioritization and functional enrichment analysis to systematically determine the molecular architecture of metabolic nutritional genomics.

The analytical strategy aimed to assess the association between genes, single-nucleotide polymorphisms (SNPs), metabolic disease traits and pathway-level biological functions. Disease-category distributions were summarized and visualized statistically to characterize them and to identify highly interconnected genes that have broad metabolic relevance. Then, network topology measures and enrichment analyses were performed to identify important molecular pathways that are involved in the biological process.

2.2 Data Source

The data analyzed in this study come from the GRPM Dataset, which is a curated nutrigenomic dataset reporting experimentally observed relationships between genes, genetic variants, food intake and metabolic disease traits (De Filippis et al., 2024). The dataset includes information related to metabolic phenotypes, gene–trait interactions, semantic similarity measures, GWAS effect sizes, and linked biomedical references.

The data set contained nutrigenomic data for cardiovascular lipid disorders, obesity, diabetes, liver-related metabolic disorders, and other metabolic phenotypes. Data fields contained gene identifiers, SNP data, disease traits, semantic similarity measures and accompanying publication references, allowing for comprehensive downstream statistical and network analyses.

2.3 Data Preprocessing and Categorization

Analytical workflows implemented in Python were used for data pre-processing. To ensure consistency in and reliability of the dataset and the analyses, duplicate records and incomplete entries were eliminated. Prior to analysis, gene names, SNP identifiers and disease-trait annotations were standardized.

The disease traits were then organized into five key metabolic clusters: cardiovascular lipid disorders, obesity, diabetes, liver-related, nonalcoholic fatty liver disease (NAFLD), and other metabolic diseases. Such classification allowed comparative evaluation of the nutrigenomic distribution for each disease and enabled visualization of the network downstream. The following summary statistics were generated per disease category: number of unique genes, SNPs, traits, semantic similarity scores, and GWAS effect size.

2.4 Network Construction and Hub-Gene Identification

A network of gene–trait interactions was created to visualize the interaction between the major nutrigenomic genes and metabolic disease traits. Network nodes were genes and disease-associated traits, while edges were known nutrigenomic associations among nodes.

The hub genes were selected by their interaction density and trait connectivity within the network built. A hub score was determined through a sum of unique SNP associations, the number of disease traits connected to the SNP and the diversity of types of disease traits. Genes with high connectivity and metabolic associations were selected as hub genes for further interpretation and enrichment analyses.

2.5 Statistical and Descriptive Analysis

The descriptive statistical analyses summarized characteristics of the overall data set and distribution of disease categories. Association strength and consistency of nutrigenomic associations were assessed by computing mean and median semantic similarity scores and GWAS effect sizes.

Disease distributions, hub-gene importance and disease-gene–trait interactions were drawn using visualization techniques such as doughnut plots, bubble plots and network diagrams. The visualizations were helpful in interpreting the overall molecular architecture and disease-specific grouping patterns in the nutrigenomic data set.

2.6 Functional Enrichment Analysis

Top-ranked hub genes from network analysis were used for functional enrichment analysis. To identify significantly enriched biological pathways and molecular functions related to the hub genes, Gene Ontology (GO) Biological Process, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Reactome pathway analyses were carried out.

The adjusted p-values and combined enrichment scores were used to evaluate enrichment significance. The resultant pathways were ordered by statistical significance and biological relevance, and key lipid-metabolism, cholesterol-transport and lipoprotein-remodeling pathways were identified for metabolic nutrigenomic regulation.

3. RESULTS

3.1 Overview of the Metabolic Nutrigenomic Dataset

A total of 144,377 metabolic nutrigenomic association records were identified and incorporated into the analytical framework. The data set included 194 unique genes, 541 SNPs, 392 disease traits and 3,535 PubMed-indexed references, which provided a significant diversity and depth of evidence around the nutrigenomics. The overall semantic consistency of the dataset was high, with a mean semantic similarity score of 0.9422, and the mean GWAS effect size was 1.0536, indicating moderate to strong genetic associations between metabolic phenotypes. The principal characteristics of the curated nutrigenomic data set are summarized in Table 1.

Table 1. Study overview of the integrated metabolic nutrigenomic dataset

Study Metric	Value
Total metabolic nutrigenomic records	144,377
Unique genes	194
Unique SNPs	541
Unique disease traits	392
Unique PubMed references	3,535
Mean semantic similarity	0.9422
Median semantic similarity	0.9328
Mean GWAS effect size	1.0536
Median GWAS effect size	0.2500

3.2 Distribution of Nutrigenomic Associations Across Metabolic Disease Categories

The associations between the metabolites and the genetics were not evenly distributed in disease categories. The category with the greatest number of records (82,430 associations) was cardiovascular lipid disorders (57.1%). The associations of NAFLD were 23.2%, and of obesity-related traits were 18.0%, as shown in Figure 1. Diabetes and other metabolic phenotypes had much lower shares, however. Lipid metabolism is the most widely studied domain of metabolic nutrigenomics, as cardiovascular lipid associations are prevalent. The significant amount of NAFLD-related information further highlights the increasing role of hepatic lipid dysregulation in precision nutrition research.

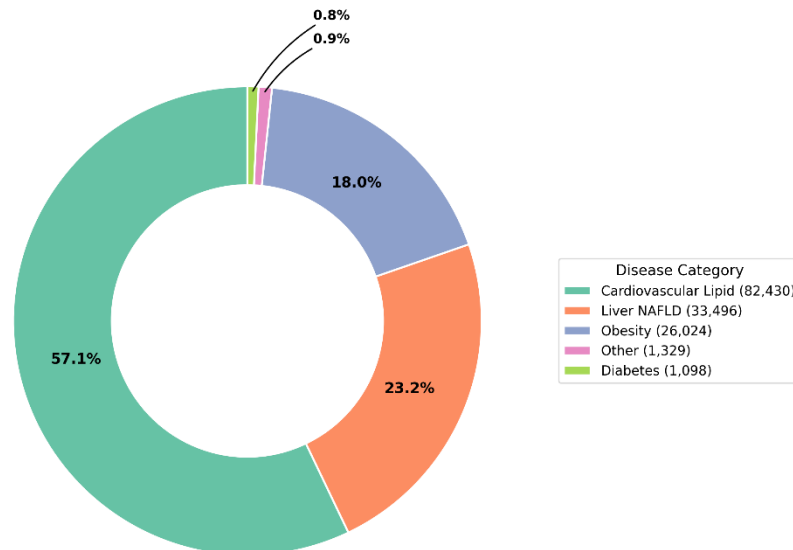


Figure 1. Distribution of nutrigenomic associations across metabolic disease categories

Disease-level summary statistics were assessed to further characterize category specific trends. The highest number of unique genes (130), SNPs (352) and disease traits (357) were found for cardiovascular lipid disorders, while the highest semantic similarity scores were found for obesity. Compared to other hepatic metabolic phenotypes, the NAFLD of the liver had the highest mean GWAS effect size (1.9776). The detailed disease category summary statistics are given in Table 2.

Table 2. Disease category summary statistics

Disease Category	Records	Unique Genes	Unique SNPs	Unique Traits	Mean Semantic Similarity	Median Semantic Similarity	Mean GWAS Effect Size	Median GWAS Effect Size
Cardiovascular Lipid	82,430	130	352	357	0.9443	0.9356	0.8945	0.1819
Diabetes	1,098	26	34	14	0.9439	0.9440	0.3688	0.0684
Liver NAFLD	33,496	8	12	4	0.9187	0.9218	1.9776	1.4000
Obesity	26,024	77	182	7	0.9647	0.9595	0.3941	0.0486
Other	1,329	27	38	10	0.9565	0.9495	0.6580	0.3800

3.3 Identification of Major Nutrigenomic Hub Genes

A few genes were found to have significantly high connectivity across metabolic traits by network-centrality analysis. The results of Figure 2 show that ZPR1 was the strongest hub gene, with a composite hub score of 261, followed by GCKR (225), APOE (194) and PCSK9 (185). These genes were linked to several SNPs, a wide range of metabolic traits and multiple disease categories. Most of the highly ranked genes were directly associated with lipid metabolism, triglycerides, lipoprotein remodeling and cholesterol transport. Other genes with significant network centrality were LPL, APOB, ANGPTL4, and CELSR2, which have significant functions in metabolic homeostasis. To sum up the detailed characteristics of the top hub genes, Table 3 has been provided.

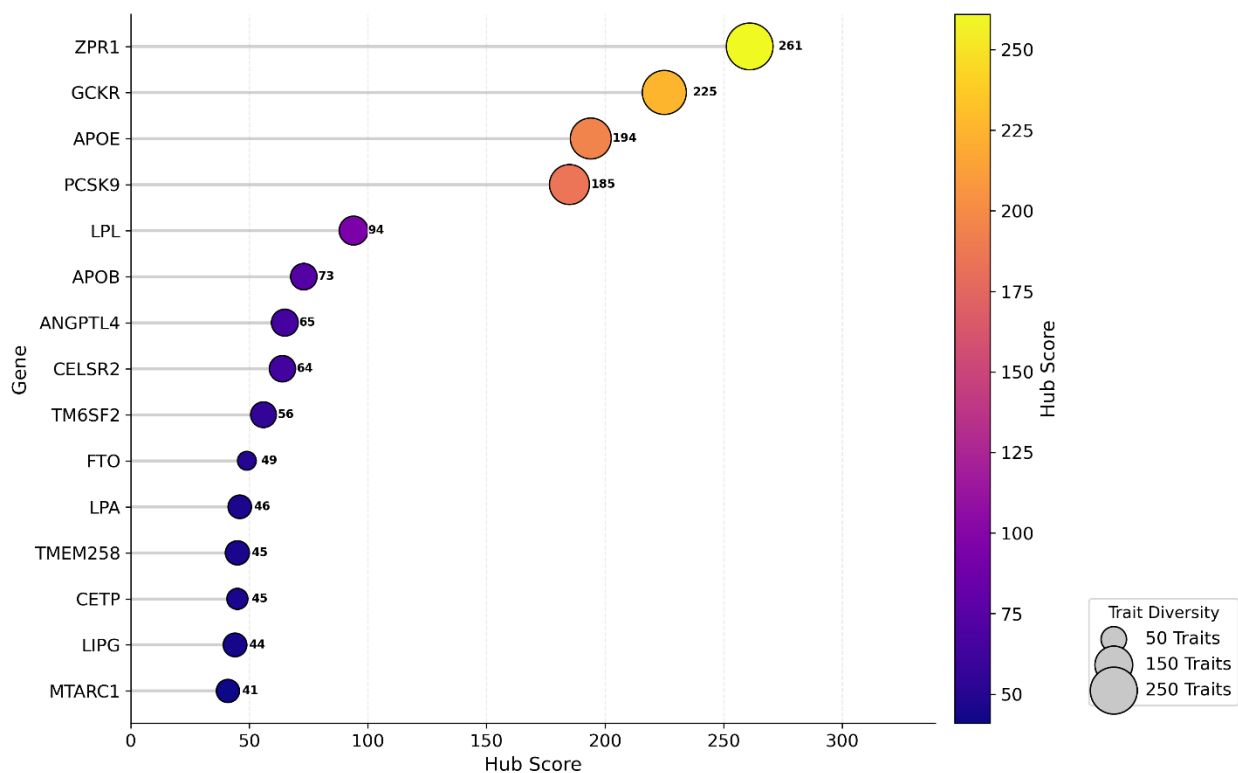


Figure 2. Top hub genes in nutrigenomic metabolic associations

Table 3. Top hub genes associated with metabolic nutrigenomic traits

Gene	Unique SNPs	Unique Traits	Disease Categories	Mean Semantic Similarity	Mean GWAS Effect Size	Hub Score
ZPR1	11	248	2	0.9302	0.4523	261
GCKR	4	216	5	0.9304	0.3292	225
APOE	8	182	4	0.9262	0.3689	194
PCSK9	11	172	2	0.9249	0.7567	185
LPL	18	74	2	0.9348	0.2793	94
APOB	14	57	2	0.9336	0.4594	73
ANGPTL4	3	60	2	0.9280	0.1776	65
CELSR2	6	56	2	0.9235	0.7689	64
TM6SF2	1	52	3	0.9301	0.5178	56
FTO	33	12	4	0.9592	0.5334	49
LPA	5	38	3	0.9202	0.1616	46
TMEM258	1	42	2	0.9238	0.0649	45
CETP	20	24	1	0.9303	0.3532	45
LIPG	4	39	1	0.9261	0.2161	44
MTARC1	3	36	2	0.9287	0.2675	41

3.4 Gene–Trait Interaction Network Analysis

The gene–trait interaction network showed a dense network of interactions between lipid-related metabolic phenotypes. Figure 3 shows the genes GCKR, ZPR1, LPA and APOE having highly connected central roles in the network, connecting several triglyceride- and cholesterol-related traits.

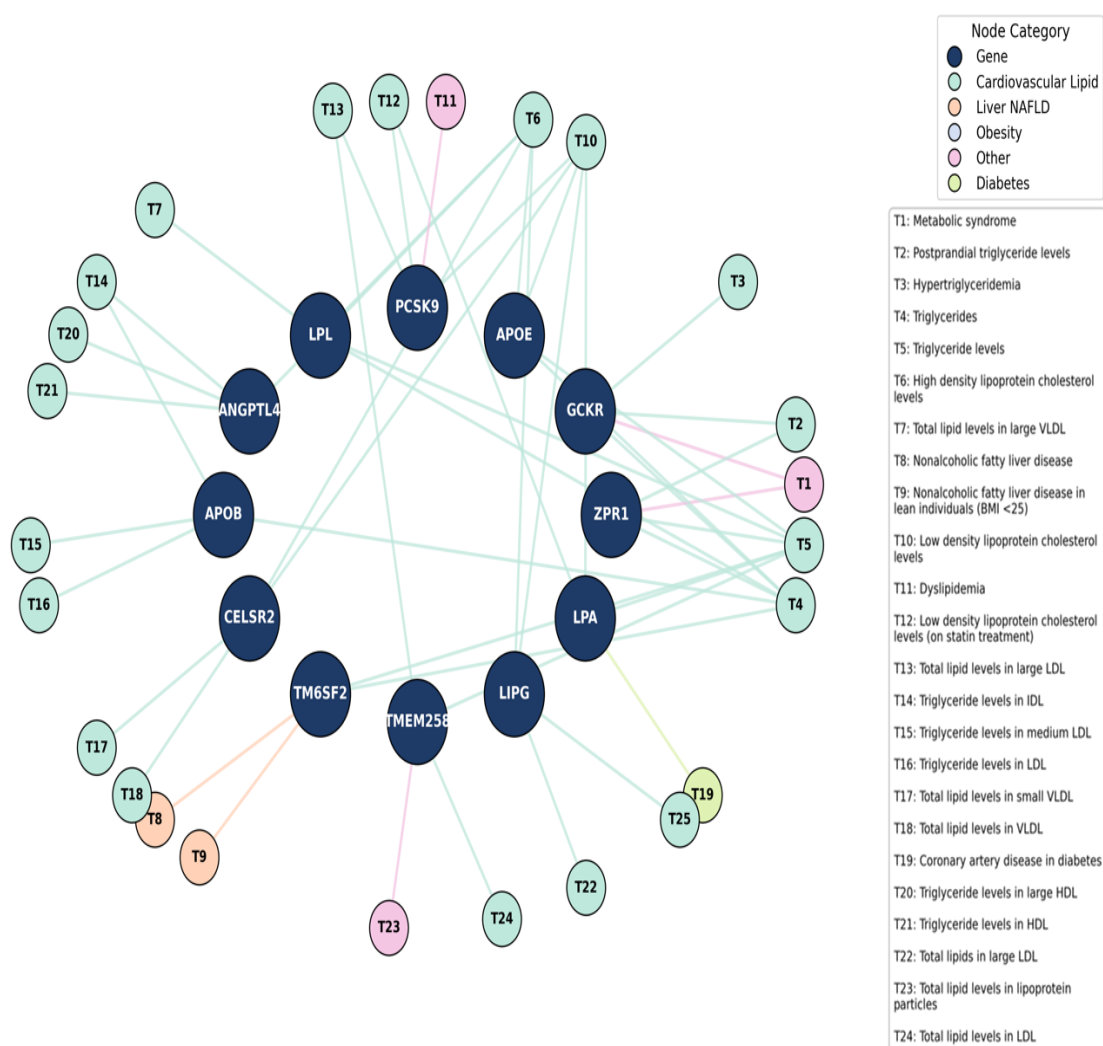


Figure 3. Gene–trait network of major nutrigenomic metabolic associations

The graph structure showed several subnetworks. The largest interaction cluster was associated with genes involved in triglyceride metabolism such as GCKR, LPL, ANGPTL4 and APOB. The traits overlapping with PCSK9, APOE and LPA were predominantly associated with cholesterol-related processes, known for their proven role in lipoprotein transport and regulation of cardiovascular risk.

Furthermore, the traits of the NAFLD showed strong interactions with TM6SF2, while the dyslipidaemic-related nodes were strongly associated with LPA and PCSK9. Based on the observed topology, there is great overlap between hepatic lipid metabolism, triglyceride regulation and cardiovascular metabolic pathways.

3.5 Functional Enrichment Analysis of Top Nutrigenomic Hub Genes

Using functional enrichment analysis, the identified nutrigenomic hub genes were found to be significantly enriched in lipid metabolism and lipoprotein-regulation pathways. Figure 4A indicates that the GO Biological Process analysis was mainly enriched with pathways related to cholesterol homeostasis, sterol homeostasis, cholesterol transport and triglyceride homeostasis, revealing high levels of biological involvement in systemic lipid regulation and lipoproteins remodeling.

As illustrated in Figure 4B, the cholesterol metabolism, fat digestion and absorption, bile secretion, and PPAR signaling pathways were mostly focused on by KEGG pathway enrichment, indicating the key roles of lipid processing and metabolic signaling pathways in the nutritional network, which are closely related to dietary lipids. Likewise, important pathways in lipid transport and lipoprotein dynamics, such as plasma lipoprotein assembly and remodeling, chylomicron clearance, HDL remodeling and small molecule transport, are also enriched in Reactome (Figure 4C), confirming the importance of lipid transport and lipoprotein dynamics in the metabolic nutrigenomic regulation. In order to provide a summary of the most significantly enriched pathways and biological processes, these pathways and processes are summarized in Table 4.

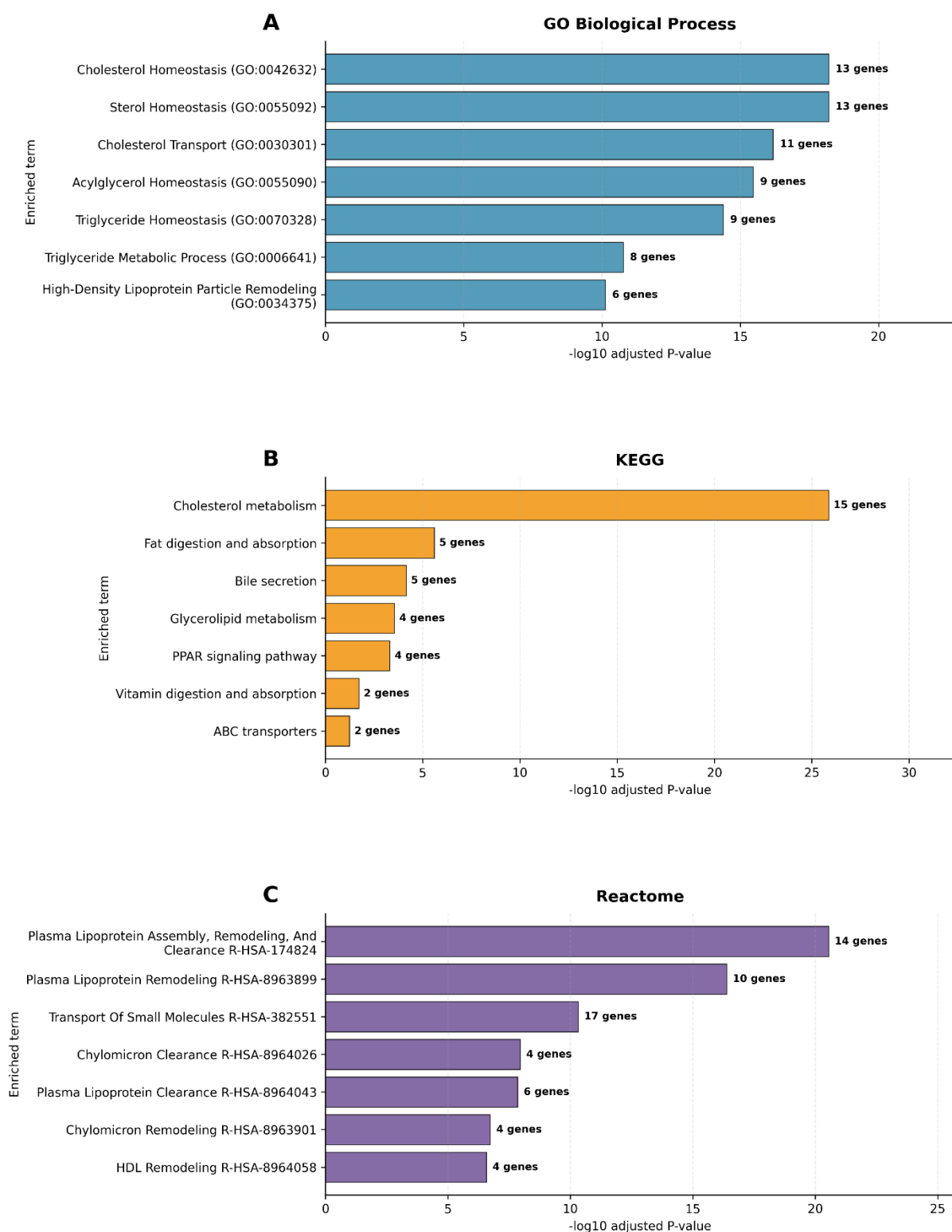


Figure 4. Functional enrichment analysis of top nutrigenomic hub genes (A) GO Biological Process enrichment, (B) KEGG pathway enrichment, (C) Reactome pathway enrichment

Table 4. Functional enrichment analysis of top nutrigenomic hub genes

Database	Enriched Term	Gene Overlap	Adjusted P-value	Combined Score
GO Biological Process	Cholesterol Homeostasis	13/72	<0.000001	5662.600
GO Biological Process	Sterol Homeostasis	13/73	<0.000001	5545.301
GO Biological Process	Cholesterol Transport	11/51	<0.000001	5977.215
GO Biological Process	Acylglycerol Homeostasis	9/24	<0.000001	11853.324
KEGG	Cholesterol metabolism	15/50	<0.000001	15563.608
KEGG	Fat digestion and absorption	5/43	0.000003	958.173

KEGG	PPAR signaling pathway	4/74	0.000496	253.414
Reactome	Plasma Lipoprotein Assembly, Remodeling, and Clearance	14/71	<0.000001	7175.484
Reactome	Plasma Lipoprotein Remodeling	10/33	<0.000001	9221.626
Reactome	Chylomicron Clearance	4/5	<0.000001	38997.873

All these results show that the identified hub genes are mainly involved in the pathways related to lipid transport, lipoprotein remodeling, and triglyceride metabolism.

4. DISCUSSION

The results suggest that metabolic nutrigenomic links are mostly focused on lipid metabolism, cholesterol transport and lipoprotein remodeling. The disease categories included the largest number of cardiovascular lipid traits, with liver NAFLD and obesity, followed, indicating a strong association of gene–diet interactions with pathways of lipid regulation and cardiometabolic risk. Diabetes associated records were relatively fewer, but they played a significant metabolic role within the data set. The hub-gene analysis also revealed that the network structure was lipid-centred, with the most interconnected genes for the various lipid, triglyceride, cholesterol, and metabolic traits being ZPR1, GCKR, APOE and PCSK9. Other genes, such as LPL, APOB, ANGPTL4, CELSR2, TM6SF2, LPA, and LIPG, were grouped into metabolic modules that were connected to the lipid transport pathway and hepatic fat metabolism. To substantiate these observations, functional enrichment analysis was performed, which highlighted significant enrichment of pathways involved in cholesterol homeostasis, triglyceride metabolism, PPAR signaling, plasma lipoprotein remodeling, clearance of chylomicron and HDL remodeling. Overall, the statistical, network and enrichment results indicated that lipid metabolism biology is a key molecular process involved in nutrigenomic effects on metabolic diseases.

The predominance of lipid-associated traits in the present analysis is similar to the results of large-scale lipidomic analyses that have identified genomic loci associated with circulating lipid variance, primarily related to lipid transport and metabolic homeostasis (Ottensmann et al., 2023). Likewise, population-based lipid genetics studies have also validated the importance of a number of known variants for blood lipid variation among ethnic groups (Bandesh et al., 2019). In the present network, APOE (apolipoprotein E), one of the most important genes that mediate lipoprotein transport and cholesterol redistribution, showed up among the most important genes in the hub. It is highly connected and consistent with previous findings that APOE is a key regulator of dyslipidemia and susceptibility to fatty liver (Nock, 2024). Similarly, the network centrality values were high for PCSK9 (proprotein convertase subtilisin/kexin type 9), which has been shown to regulate LDL receptor degradation and plasma cholesterol levels (Masood et al., 2024), and this further corroborates its important role in inherited and complex lipid disorders.

An important regulator of hepatic glucose and triglyceride metabolism, GCKR (glucokinase regulatory protein), had widespread associations with various metabolic traits. This is consistent with previous reports that GCKR is a molecular connection between glucose homeostasis, triglyceride regulation and susceptibility to NAFLD (Zhang et al., 2023). Important NAFLD-related associations were also observed for the genes TM6SF2 (transmembrane 6 superfamily member 2) and PNPLA3 (patatin-like phospholipase domain-containing protein 3), which play a key role in hepatic lipid handling, as indicated by current evidence of their genetic associations with NAFLD (Pei & Goh, 2025).

An appetite-regulating gene called FTO (fat mass and obesity associated gene) was found in the obesity associated hub genes. This is consistent with earlier studies showing a correlation between FTO polymorphisms and consumption of fat and sugar in dietary habits among individuals with obesity-related metabolic dysfunction (Poosri et al., 2024). Enrichment of the pathways involved in VLDL remodeling, chylomicron clearance, and lipoprotein transport further supports a key role of triglyceride-rich lipoproteins in the progression of cardiometabolic disease, as suggested by mechanistic studies (Lee et al., 2022). Further, the key hyper-enrichment of pathways related to PPAR signaling pathways further corroborates the well-acknowledged function of nutrient-sensitive transcriptional regulators in regulating lipid metabolism, inflammation, and cardiovascular metabolic function (Montaigne et al., 2021). Last, the significant enrichment of dyslipidemia-related pathways and genes is consistent with the current knowledge of atherogenic dyslipidemia as a genetically determined part of metabolic syndrome, which is related to the metabolism of triglyceride-rich lipoproteins, HDL remodeling and LDL metabolism (Butnariu et al., 2023).

The results of these studies have relevance to the field of personalised nutrition and the prevention of metabolic diseases. Lipid-centered hub genes indicate that genetic testing may be useful for the stratification of individuals based on their susceptibility to dyslipidemia, NAFLD, obesity associated metabolic dysfunction and cardiometabolic risk. The genes examined in this study, including GCKR, APOE, PCSK9, LPL, APOB and TM6SF2, may be viable candidates for future genotype-sensitized dietary studies, which could include lipid, cholesterol regulation and hepatic fat accumulation. The pathway findings also indicate that lipid transport, the metabolism of triglycerides, processing of lipids by bile and PPAR-mediated nutrient signaling would be targets for personalized nutrition strategies. The results are not limited to any single nutrient or gene, and they favor a systems-level approach to diet and nutrition, with the recommendations based on gene networks and pathway-

level metabolic functions. This could provide a more accurate biological targeting for nutrition interventions for metabolic disease prevention.

Some restrictions need to be taken into account. The analysis was conducted using a curated secondary data set, which may affect the findings, as completeness and quality of the original data set may vary. The study also revealed associations and patterns of the networks rather than causal mechanisms. Furthermore, there were fewer categories of diseases represented, especially the diabetes category, compared to cardiovascular lipid and NAFLD categories.

Further studies with clinical cohorts with detailed dietary intake, genotype, lipidomic and metabolic phenotype data should confirm these results. A combination of multi-omics layers, such as transcriptomics, metabolomics, microbiome profiles and dietary assessment (longitudinal) would further elucidate the role of nutrigenomic variants on metabolic pathways over time. Computationally identified hub genes and enriched pathways could also be validated with experiments, and provide valuable information to translate this into actionable personalized nutrition strategies.

5. CONCLUSION

Lipid metabolism, cholesterol transport, triglyceride regulation, and lipoprotein remodeling were the main themes in the metabolic nutrigenomic associations. The major disease category was cardiovascular lipid traits, followed by NAFLD and obesity, suggesting that lipid regulatory pathways provide a large molecular connection between genetic variation, nutrition and metabolic disease risk. ZPR1, GCKR, APOE and PCSK9 were highly connected genes, with other genes (LPL, APOB, ANGPTL4, TM6SF2, LPA and LIPG) contributing to interconnected metabolic modules. The gene–trait network revealed that metabolic phenotypes are not distinct and have common molecular drivers, especially in the triglyceride, cholesterol, hepatic lipid, and cardiometabolic pathways. These areas were confirmed by functional enrichment to be of central importance: cholesterol homeostasis, PPAR signaling, clearance of chylomicrons, remodeling of HDL, and regulation of plasma lipoproteins. The results suggest that there is a need for a systems approach to nutrigenomics, where interventions to promote personalized nutrition should take into account the action of gene networks and pathway-level processes rather than the action of individual genes. These findings could be translated to precision nutrition and prevention of metabolic diseases via future validation with clinical, dietary, and multi-omics datasets.

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