Article

Genetic Modulation of LDL-C and Triglyceride Response to Mediterranean-Style Diet: Whole-Exome Evidence with a Focus on Plasma Lipoprotein Pathways

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Abstract

Background/Objectives: Inter-individual variability in lipid response to dietary modification highlights the need for precision nutrition. Current evidence is fragmented and primarily based on a limited set of historical candidate genes. To address these gaps and facilitate broader discovery, this study investigated whether exome-wide genetic variation is associated with changes in LDL cholesterol (LDL-C) and triglycerides (TAG) following a Mediterranean-style diet. **Methods:** A longitudinal study was conducted with 51 dyslipidemic patients who underwent a 2–6 month Mediterranean-style dietary intervention. High-depth whole-exome sequencing (mean 112×) was performed, and a two-tier analytical approach was used: an exploratory exome-wide association analysis to identify novel loci, and a targeted gene-level analysis of the 'Plasma Lipoprotein Assembly, Remodeling, and Clearance' pathway to prioritize biologically plausible signals. **Results:** The intervention resulted in significant reductions in LDL-C (mean -33.4 mg/dL) and TAG (-17.9 mg/dL). genome-wide association study (GWAS) identified top signals in *ABCA2* (LDL-C response, $p = 2.05 \times 10^{-5}$) and ABCA7 (TAG response, $p = 5.48 \times 10^{-5}$). Targeted pathway analysis revealed the strongest gene-level associations for LDL-C change in APOC3, APOC2, and adaptor protein complex subunits AP2A1 and AP2A2 (Simes p = 0.007–0.018; false discovery rate (FDR) = 0.21), while APOB (Simes p = 0.010; FDR = 0.46) was the top signal for TAG change. These loci implicate convergent mechanisms involving triglyceride-rich lipoprotein remodeling and clathrin-dependent receptor trafficking. **Conclusions:** The results suggest that genetic modulation of dietary lipid response involves distributed effects within biologically coherent pathways rather than single high-impact variants. By combining exploratory genome-wide screening with process-focused gene prioritization, this demonstrates a pragmatic framework for identifying functional candidates to inform genetically guided dietary recommendations.

Keywords: nutrigenomics; Mediterranean diet; whole exome sequencing; LDL-C; triglycerides; lipoprotein metabolism; gene-diet interactions

1. Introduction

Dyslipidemia remains a central, modifiable driver of atherosclerotic cardiovascular disease risk, and dietary change is a first-line lifestyle strategy to lower low-density lipoprotein cholesterol (LDL-C). Among the most studied dietary patterns, Mediterranean-style diets have shown cardiovascular benefit in both primary and secondary prevention settings [1,2]. However, lipid responses to dietary modification are notably heterogeneous. Under comparable guidance, the degree of improvement varies substantially, with some patients showing little benefit or even paradoxical worsening. This inter-individual variability underscores the rationale for precision nutrition approaches [3].

Nutrigenomics investigates the interaction between diet and genetic variation in shaping disease risk and therapeutic response, with the aim of explaining inter-individual variability in metabolic traits. However, much of the current evidence base remains centered on candidate-gene studies. While interactions have been reported for well-studied loci such as APOE and CETP [4,5], evidence for other loci (e.g., APOA5, ABCG5) remains sparse, limiting inference beyond specific study settings [6,7]. Research often remains constrained to a small set of historical loci, leaving a fragmented evidence base that is difficult to consolidate. Moreover, as current evidence is heavily skewed toward specific populations, generalizability remains a critical gap [8].

To address these limitations, genome-wide approaches are essential for broader, hypothesis-free discovery, enabling the identification of novel variants beyond restricted candidate lists. We conducted an exploratory study to examine whether genetic variation is associated with blood lipid changes in a clinical cohort receiving Mediterranean-style dietary guidance. To capture the full spectrum of variation, we utilized a two-tier strategy: first, an exome-wide analysis of lipid response to facilitate broad locus discovery; and second, a targeted analysis of a priori selected genes defined within the lipoprotein metabolism pathway to enhance sensitivity for biologically plausible signals. We focused primarily on LDL-C response given its central role in atherosclerotic risk, with TAG (triglycerides) analyzed as a secondary lipid trait.

2. Materials and Methods

Ethics and Participants

The study protocol was approved by the Ilia State University Bioethics Committee (Approval No. R/215-24, 01.07.2024) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, and clinical data were anonymized prior to analysis. Patients identified with elevated LDL cholesterol at an initial visit were enrolled during their subsequent clinical follow-up. Eligible individuals had completed 2–6 months of a prescribed Mediterranean-style diet and had both baseline and follow-up lipid profiles available.

Inclusion criteria comprised informed consent, documented adherence to dietary recommendations, availability of lipid data for baseline and follow-up time points, and euthyroid status. Exclusion criteria included lipid-lowering medication use, bariatric surgery, major weight change, diabetes mellitus, established cardiovascular disease, secondary or hereditary dyslipidemia, pregnancy or lactation, severe comorbidities (e.g., active malignancy, renal failure, or hepatic insufficiency), uncontrolled hypertension, heavy alcohol intake, or any condition impairing participation. A total of 52 participants were included in the analysis.

Clinical Data

LDL cholesterol (LDL-C) and triglycerides were measured in a single certified laboratory (Diacor, Tbilisi, Georgia) at baseline and after dietary intervention. Analysis was performed on venous blood serum using a fully automated Cobas c111 analyzer (Roche Diagnostics). LDL-C was determined using the LDL-Cholesterol Gen.3 kit (Roche Diagnostics , Ref: 7005806190) via a homogeneous enzymatic colorimetric assay. Triglycerides were quantified using the standard Roche Triglycerides kit (Ref: 04657594190) via an enzymatic colorimetric method. The interval between the two assessments was 2–6 months. Reference ranges were defined as <130 mg/dL for LDL-C and <150 mg/dL for triglycerides.

DNA Extraction and Sequencing

Genomic DNA was extracted from peripheral blood using the Qiagen QIAamp DNA Blood Mini Kit (Ref: 51106). DNA purity and concentration were evaluated using Nanodrop spectrophotometry; samples meeting provider requirements were lyophilized and shipped to the sequencing facility. Whole-exome sequencing was performed by BMK Gene (China) using the Agilent SureSelect V6 capture kit. Libraries were prepared according to manufacturer protocols and sequenced on an Illumina NovaSeq platform with paired-end 150 bp reads. Base calling was performed using Illumina Casava v1.8.

Data Processing and Variant Analysis

Low-quality reads were removed if they contained adaptor contamination, more than 10% undetermined bases, or more than 50% low-quality bases. Clean reads were aligned to the human reference genome GRCh38 using BWA-MEM with default parameters. Post-alignment processing followed GATK Best Practices using standard default settings, including duplicate removal (Picard), base-quality score recalibration, and indel realignment. Variant calling was performed using GATK HaplotypeCaller (default configuration), and high-confidence variants were retained following Variant Quality Score Recalibration. Variants were annotated using ANNOVAR with default databases [9].

Statistical Analysis

Genotype data processing and genome-wide association analyses were conducted using PLINK v2.0 [10]. Downstream statistical analyses were performed in the R computing environment (version 4.1.1). Data management was performed using data.table [11]. Genomic annotations and gene coordinates were retrieved using biomaRt [12], and GWAS diagnostic plots were generated using qqman [13]. Generative AI tools (Gemini, Google) were utilized to assist in the drafting and debugging of R scripts used for data processing and visualization. All scripts used for quality control, genome-wide association analyses, targeted pathway analysis, and figure generation are publicly available and archived on Zenodo (https://doi.org/10.5281/zenodo.18312269).

Variants were filtered based on strict quality control criteria: minor allele frequency (MAF) > 0.01, genotype call rate > 0.90, and Hardy–Weinberg equilibrium $p > 1 \times 10^{-6}$. To account for population stratification, linkage disequilibrium (LD) pruning was performed (200-variant window, $r^2 < 0.1$) and principal component analysis (PCA) was conducted. Relatedness was assessed using the KING kinship coefficient [14]; one first-degree relative (kinship > 0.177) was identified and excluded to ensure sample independence prior to association testing.

Genome-wide association analyses were conducted separately for LDL-C and TAG using generalized linear models (GLM) in PLINK 2.0 under an additive genetic model. Linear regression was performed on the Winsorized change in lipid levels (mean ± 3 standard deviations) to minimize the impact of outliers while preserving interpretable effect estimates. All models were adjusted for age and sex. Nominal p-values and Benjamini–Hochberg FDR adjusted p-values are reported for the prioritization of candidate loci.

Targeted Gene Analysis

In addition to the genome-wide analysis, a targeted analysis was performed on genes within the Reactome pathway "Plasma Lipoprotein Assembly, Remodeling, and Clearance" (R-HSA-174824). This gene list was defined a priori as a curated set of genes directly involved in lipoprotein metabolism. Variants mapping to these genes (GRCh38 gene coordinates) were extracted from the post-QC dataset. Variants were further filtered to retain only those with a minor allele count (MAC)

> 3 and presence in at least 2 individuals. To provide a gene-level significance metric, p-values for variants within each locus were summarized using the Simes method [15]. This approach tests the global null hypothesis (that at least one variant is associated) and remains valid under the linkage disequilibrium structures typical of genomic data [16]. Gene-level p-values were subsequently adjusted for multiple comparisons using the Benjamini–Hochberg FDR.

3. Results

Sequencing Performance and Data Quality

Whole-exome sequencing produced usable data for all 52 samples, with no exclusions due to sequencing failure or insufficient quality. The mean sequencing depth across target regions was 111.9x, the proportion of bases with Q30 quality was 96.87%, and the mean mapping efficiency was approximately 99.9%. Variant calling identified approximately 135,000–156,000 SNPs per sample. Relatedness assessment identified one first-degree related pair (kinship > 0.177); one individual was excluded to ensure sample independence. Principal component analysis (PCA) on LD-pruned variants demonstrated a homogenous population structure without significant stratification outliers. Consequently, statistical models were adjusted for age and sex to preserve statistical power in this exploratory cohort.

Participant Characteristics

Fifty-one participants were included in the final analysis (28 females, 23 males). Baseline characteristics are summarized in Table 1. Mean age was 48.0 ± 12.7 years, and the mean interval between baseline and follow-up assessments was 5.0 ± 2.2 months; these did not differ by sex (p = 0.158 and p = 0.308, respectively). Baseline LDL-C was 149.5 ± 27.4 mg/dL and decreased to 116.1 ± 22.7 mg/dL at follow-up, with a mean change of -33.4 ± 25.1 mg/dL; LDL measures and change were not significantly different between females and males (all p >= 0.295). In contrast, absolute triglyceride concentrations were significantly higher in males at both baseline and follow-up (p = 0.033 and p = 0.018, respectively). However, the response to the intervention was similar in both groups; the magnitude of triglyceride change did not differ by sex (p = 0.736).

Table 1. Baseline and Follow-Up Characteristics of Study Participants.

	Overall (N=51)	**Female (N=28)**	**Male (N=23)**	**P-value**
Age (years)	48.0 ± 12.7	50.3 ± 12.5	45.2 ± 12.6	0.158
Interval (months)	5.0 ± 2.2	4.7 ± 2.4	5.3 ± 1.9	0.308
Baseline LDL-C (mg/dL)	149.5 ± 27.4	149.6 ± 29.1	149.3 ± 25.8	0.975
Follow-up LDL-C (mg/dL)	116.1 ± 22.7	113.0 ± 21.4	119.9 ± 24.2	0.295
ΔLDL-C (mg/dL)	-33.4 ± 25.1	-36.6 ± 23.2	-29.5 ± 27.2	0.328
Baseline TAG (mg/dL)	148.5 ± 67.0	129.4 ± 44.4	171.8 ± 82.2	0.033
Follow-up TAG (mg/dL)	130.6 ± 68.0	108.8 ± 37.3	157.2 ± 86.4	0.018
ΔTAG (mg/dL)	-17.9 ± 57.3	-20.6 ± 28.9	-14.6 ± 80.2	0.736

Note: Values are reported as mean ± SD. P values are from Welch's independent-samples t tests (female vs. male). LDL-C = low-density lipoprotein cholesterol. TAG = triglycerides.

Genome-Wide Association Results

Quantile-quantile (QQ) plots of the observed versus expected p-values demonstrated no evidence of genomic inflation (Figure 1), with genomic control lambda values of 0.987 for LDL-C change and 0.965 for TAG change. Additionally, principal component analysis confirmed that population structure did not significantly bias the observed lipid responses (Figure S1). Full linear model coefficients, including the effects of age and sex covariates, are provided in Table S1.

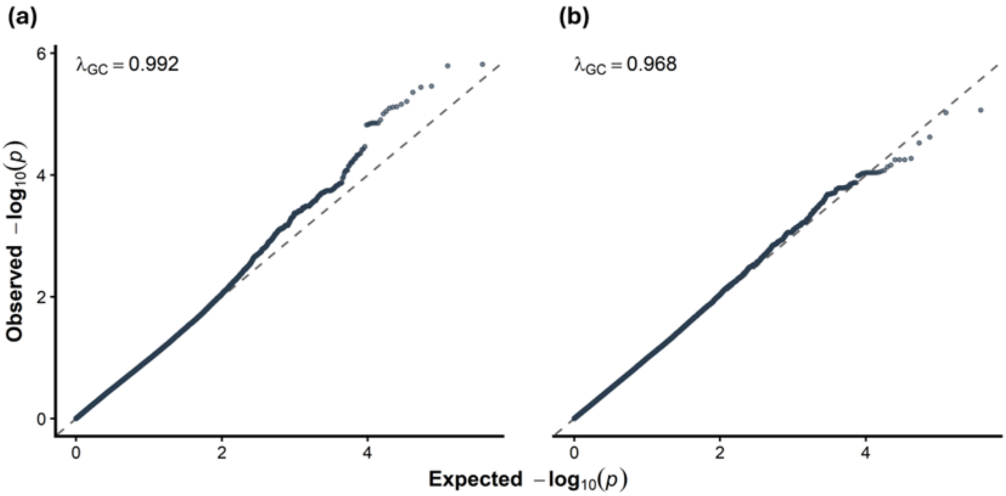

Figure 1. Quantile–quantile (QQ) plots for exploratory GWAS of lipid response outcomes. (**a**) Observed versus expected $-\log_{10}(p)$ values for change in LDL-C (ΔLDL-C), showing a genomic inflation factor (λGC) of 0.992. (**b**) Observed versus expected $-\log_{10}(p)$ values for change in triglycerides (ΔTAG), showing a λGC of 0.968.

No individual variant reached the genome-wide significance threshold ($p < 5 \times 10^{-8}$). However, the top suggestive signals ($p < 10^{-5}$) mapped to loci with established roles in lipid trafficking (Figure 2). For LDL-C change, the strongest associations were observed in *UGT2B11* ($p = 2.55 \times 10^{-6}$) and *ABCA2* ($p = 2.05 \times 10^{-5}$), an ATP-binding cassette transporter involved in intracellular sterol homeostasis (Table S2; **Supplementary Data**). For TAG change, top signals included *IMPDH1* ($p = 7.56 \times 10^{-6}$) and *ABCA7* ($p = 5.48 \times 10^{-5}$), a functional homolog of the cholesterol efflux pump *ABCA1* (Table S3; **Supplementary Data**).

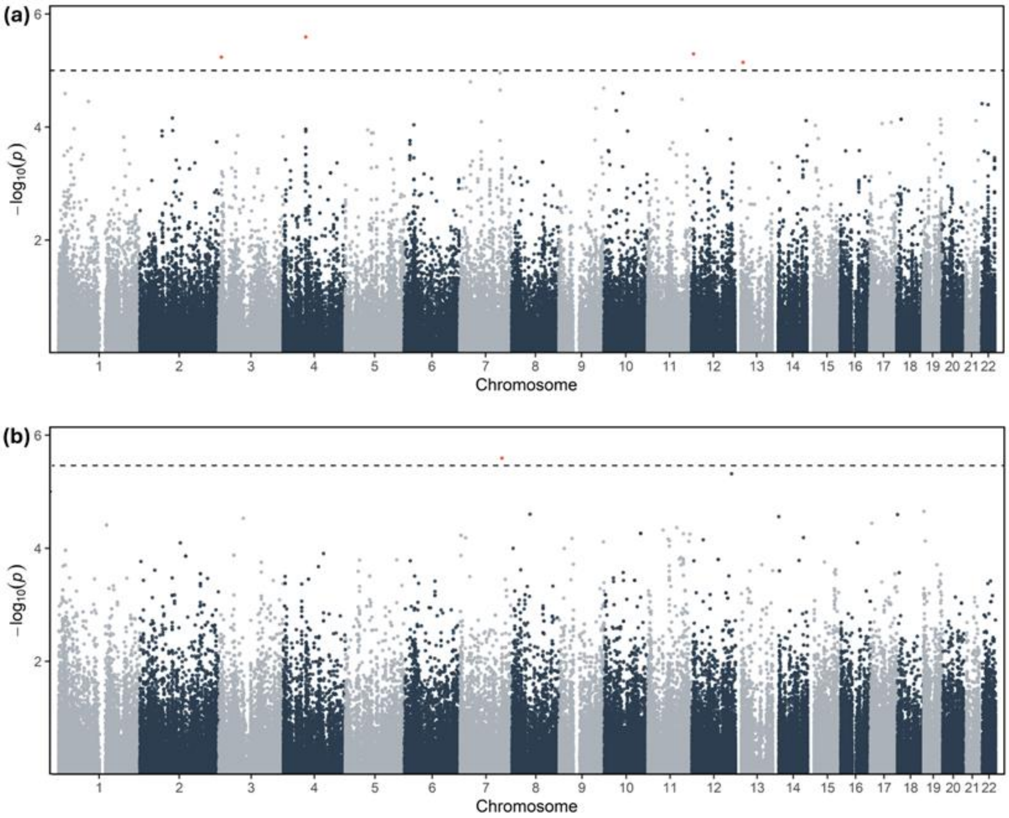

Figure 2. Manhattan plots for the exploratory GWAS of lipid response outcomes. (**a**) Exploratory GWAS of change in LDL-C (ΔLDL-C). (**b**) Exploratory GWAS of change in triglycerides (ΔTAG). The y-axis displays the

$-\log_{10}(p)$ value for each variant, and the x-axis represents the chromosomal position (autosomes 1–22). The dashed horizontal line indicates the exploratory (suggestive) significance threshold ($p = 1 \times 10^{-5}$).

Targeted Gene Analysis Results

For the change in LDL-C (Delta-LDL-C), the strongest gene-level association was observed for *APOC3* (Simes p = 0.007; FDR = 0.21). Significant associations were also identified in *AP2A2* (Simes p = 0.014; FDR = 0.21), *AP2A1* (Simes p = 0.018; FDR = 0.21) and *APOC2* (Simes p = 0.018; FDR = 0.21). For the change in triglycerides (Delta-TAG), the top association signal was identified in *APOB* (Simes p = 0.010; FDR = 0.46). Complete lists of all associations are provided in **Supplementary Data.** While gene-level associations did not reach the strict false discovery rate threshold of FDR-adjusted $p < 0.05$, nominal associations were observed in multiple loci within the pathway. Figure 3 displays the regional association plots and genotype-stratified boxplots for these loci, illustrating the distribution of lipid changes among genotype groups.

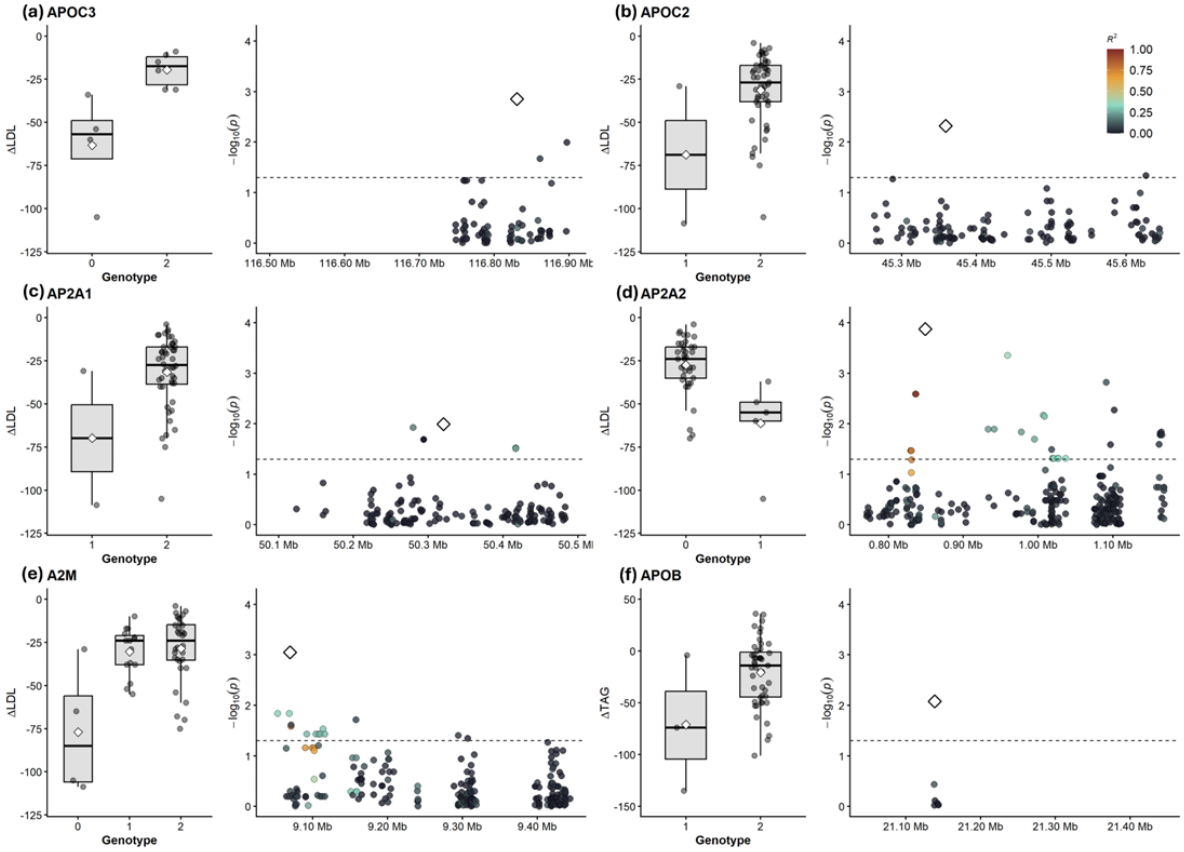

Figure 3. Regional association signals and genotypic effects for top targeted hits. (**a**) *APOC3*; (**b**) *APOC2*; (**c**) *AP2A1*; (**d**) *AP2A2*; (**e**) *A2M*; (**f**) *APOB*. For each locus, the left panel displays boxplots of the lipid change (ΔLDL-C or ΔTAG) stratified by genotype (0 = homozygous reference, 1 = heterozygous, 2 = homozygous alternate), where diamonds represent the group mean. The right panel shows the regional association plot with the strength of association ($-\log_{10}p$) versus genomic position. The horizontal dashed line indicates the nominal significance threshold ($p < 0.05$). Points are colored based on linkage disequilibrium (r^2) relative to the lead variant.

4. Discussion

Principal Findings

In this exploratory study, we examined whether genetic variation contributes to inter-individual differences in lipid response to Mediterranean-style dietary guidance. We identified suggestive exome-wide signals and coherent nominal associations within a curated lipoprotein pathway. Specifically, we observed gene-level signals in APOC3, APOC2, AP2A1, and AP2A variants. Our results support a polygenic model involving biologically coherent lipid metabolic pathways, consistent with current nutrigenetic frameworks [17]. While the absence of significant genome-wide associations is expected in exploratory settings, the absence of genomic inflation indicates that the observed signals reflect real variation suitable for prioritization.

Biological Interpretation

Prioritized loci of diet-induced LDL-C reduction point to two convergent mechanisms: triglyceride-rich lipoprotein (TRL) remodeling and receptor trafficking. Regarding TRL processing, associations were observed in APOC3 and APOC2. APOC3 inhibits LPL activity and delays hepatic uptake of TRL remnants, and loss-of-function variation is associated with reduced remnant cholesterol and lower LDL-C [18,19]. APOC2 is required for LPL activation and efficient TRL lipolysis, a prerequisite for remnant clearance and subsequent LDL particle generation [20]. These opposing roles support a model in which genetic differences in TRL processing modulate LDL-C response. Given that diets rich in monounsaturated and polyunsaturated fatty acids upregulate LPL activity [21], we propose that genetic variation in APOC2 and APOC3 may modulate the magnitude of this diet-induced increase in lipoprotein flux.

Concurrently, associations were observed in AP2A1 and AP2A2, which encode α-subunits of the adaptor protein complex-2 (AP-2). AP-2 is a central mediator of clathrin-dependent endocytosis and is required for the efficient internalization and recycling of the LDL receptor in hepatocytes [22,23].

Study Design and Analytical Strategy

To maximize discovery, we employed biologically informed hypothesis restriction [24], prioritizing functional pathway coherence over binary significance thresholds [25]. Because baseline lipid levels are already determined by a participant's genetic profile, treating them as a control variable introduces collider bias. Effectively, adjusting for baseline removes the very genetic pathway we aim to observe, potentially masking or distorting the true gene–diet interaction signal [26,27]. This rigorous statistical approach, supported by high-depth exome sequencing (mean 111.9×), ensures that identified signals reflect genuine biological variation rather than technical artifacts.

Strengths and Limitations

This study combines deep genetic data with a controlled dietary intervention and a biologically informed analytical framework, enabling the investigation of genetic modifiers of lipid response. The use of both exploratory genome-wide screening and process-focused gene prioritization represents a balanced strategy that emphasizes biological coherence while avoiding overinterpretation of single-variant associations. Several limitations should be acknowledged. Dietary exposure was assessed within a clinical intervention setting rather than through detailed quantitative intake measures, and the cohort composition limits inference beyond the studied population. As a result, the identified associations should be interpreted as hypothesis-generating.

5. Conclusions

In conclusion, this study indicates that genetic modulation of lipid responses to dietary intervention is characterized by modest, distributed effects that align with biologically coherent processes rather than single high-impact variants. By integrating exploratory genome-wide analyses with process-focused gene prioritization, we demonstrate a pragmatic framework for interpreting nutrigenomic intervention data under realistic constraints. These findings emphasize the value of biologically informed approaches for advancing our understanding of inter-individual dietary response. Future studies with larger, more ancestrally diverse cohorts and precise dietary intake quantification will be essential for replicating and refining these findings. Ultimately, such work could inform the development of genetically guided dietary recommendations.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: Population structure and assessment of lipid response confounders; Table S1: Linear model coefficients; Table S2: Top single-variant associations for ΔLDL-C (top 20); Table S3: Top single-variant associations for ΔTAG (top 20). Supplementary Data: Excel file containing the extended top 100 genome-wide association signals and full targeted gene analysis results (Sheets 1–4).

Author Contributions: Conceptualization, S.I., N.C., R.S., V.L. and Z.K.; methodology, S.I., N.C., R.S. and V.L.; software, S.I. and V.L.; validation, S.I., N.C., R.S. and V.L.; formal analysis, S.I., N.C. and V.L.; investigation, S.I., N.C. and D.A.; resources, S.I., N.C. and D.A.; data curation, S.I., N.C. and D.A.; writing—original draft preparation, S.I., N.C. and M.K.; writing—review and editing, M.K., V.L., R.S., D.A. and Z.K.; visualization, S.I., and V.L.; supervision, R.S., V.L. and Z.K.; project administration, S.I.; funding acquisition, S.I. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethics Committee of Ilia State University (Approval No. R/215-24, 01.07.2024).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The analysis code used in this study is publicly available on GitHub (https://github.com/saba966/Nutrigen_LDL_GWAS) and archived on Zenodo (https://doi.org/10.5281/zenodo.18312269). Individual-level genomic and clinical data contain sensitive human information and are therefore not publicly available; de-identified data may be made available from the corresponding author upon reasonable request and subject to ethical approval.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

LDL-C	Low-Density Lipoprotein Cholesterol
TAG	Triglycerides
GWAS	Genome-Wide Association Study
WES	Whole-Exome Sequencing
LD	Linkage Disequilibrium
FDR	False Discovery Rate
MAF	Minor Allele Frequency
PCA	Principal Component Analysis
QC	Quality Control
QQ	Quantile-Quantile
TRL	Triglyceride-Rich Lipoprotein
LPL	Lipoprotein Lipase

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