

Genetic variation in MYLIP is associated with lipid, thyroid, liver, and hematologic traits in women: evidence from The Trøndelag Health Study and UK Biobank

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Abstract

Despite the established role of *MYLIP* in lipid regulation, its contribution to cardiovascular disease (CVD) susceptibility has not been fully elucidated, and sex-specific effects in women remain unclear. We aimed to investigate whether genetic variation in *MYLIP* is associated with cardiovascular disease (CVD) risk, cardiometabolic traits, and female-specific risk factors in women. We analyzed 46,071 women from the Trøndelag Health Study (HUNT) and 220,429 women from the UK Biobank (UKB). Genetic variants in *MYLIP* were tested for association with CVD outcomes, biomarkers and risk factors at FDR < 0.05. No significant associations were observed between *MYLIP* variants and CVD outcomes after multiple testing correction, although suggestive associations were observed for hyperthyroidism, hypothyroidism, dilated and hypertrophic cardiomyopathy, myocardial infarction, stroke, coronary artery disease, and hypertension. *MYLIP* variants were associated with 17 traits in HUNT; 10 of 11 available phenotypes replicated in UKB, including lipid traits (LDL cholesterol, cholesterol, triglycerides), thyroid-stimulating hormone, liver enzymes (ASAT, ALAT, albumin), and hematologic markers (eosinophils, lymphocytes, nucleated red blood cells). *MYLIP* shows robust associations with lipid, liver, hematologic, and thyroid traits in women. Despite no direct CVD association, the results highlight *MYLIP*'s pleiotropic role in metabolic pathways relevant to cardiovascular health in women.

Introduction

The *MYLIP* gene (myosin regulatory light chain interacting protein), also known as *IDOL* (inducible degrader of the LDL receptor), encodes an E3 ubiquitin ligase that regulates lipid metabolism by promoting degradation of the low-density lipoprotein receptor (LDLR) and related receptors^{1–3}. Through this pathway, *MYLIP* influences circulating LDL cholesterol (LDL-c) levels. Several large-scale genetic studies on lipid traits have identified variants within the *MYLIP* locus, particularly total cholesterol and LDL-c^{4–7}. Despite the central role of LDL-c as a causal risk factor for cardiovascular disease (CVD), direct evidence linking *MYLIP* genetic variation to CVD outcomes remains limited.

Beyond lipid metabolism, *MYLIP* has been implicated in several other biological processes, including hypoxia response, myotube morphogenesis, neurite outgrowth, brain plasticity and learning, as well as diet-induced obesity^{8–12}, and emerging data suggest that *MYLIP* may exert sex-specific effects on cardiometabolic physiology. Previously, the genetic variant rs3757354 has been associated with aerobic fitness in women, a strong predictor of CVD risk, potentially through disruption of an estrogen response element near the *MYLIP* locus¹³. This variant was also linked to favorable metabolic traits in women, including lower waist circumference, BMI, visceral fat, fat percentage, and C-reactive protein (CRP) levels, along with reduced need for cholesterol-lowering treatment. Another study has found the same variant to be associated with improved lipid profiles (lower total cholesterol, higher HDL cholesterol) in women, with no corresponding effects observed in men¹⁴. Furthermore, rs3757354 is linked to differential *MYLIP* expression in rat hearts, where higher expression correlates with smaller cardiac size. Similarly, sex-specific associations between *MYLIP* and cardiac contractile function have been reported¹⁵. Together these findings highlight the potential for sex-specific physiological effects of *MYLIP* genetic variation on several CVD risk factors, which collectively might influence CVD risk in a sex-dependent manner.

The importance of investigating *MYLIP* specifically in women is underscored by persistent sex disparities in cardiovascular medicine. More women than men now die of CVD in Europe, and substantial differences exist between the sexes in CVD prevalence, clinical presentation, management strategies, and outcomes^{16–19}. These

disparities reflect sex-specific pathophysiologic features that may require tailored approaches for diagnosis and treatment. Emerging evidence suggests that women may have distinct genetic and hormonal regulation of lipid metabolism compared with men^{20,21}. Sex-specific analyses have identified differences in the genetic determinants of lipid traits and in how these translate to cardiovascular risk. Moreover, thyroid function and liver metabolism, both of which are influenced by sex hormones, are known to interact with lipid homeostasis and may represent additional pathways through which *MYLIP* exerts its effects^{22,23}. Despite this, few studies have systematically examined the role of *MYLIP* in women, particularly in relation to cardiovascular and metabolic phenotypes beyond traditional lipid measures.

In the present study, we conducted a comprehensive investigation of associations between genetic variants in or near *MYLIP* and a wide range of cardiometabolic traits, female-specific factors, and disease outcomes in women, using data from two large population-based cohorts: the Trøndelag Health Study (HUNT) and the UK Biobank (UKB). Specifically, we aimed to (i) assess associations between *MYLIP* variants and cardiovascular disease outcomes, (ii) identify risk factor phenotypes significantly associated with *MYLIP*, and (iii) validate findings across cohorts. By integrating large-scale genetic data with detailed phenotypic information, we sought to provide a comprehensive understanding of the role of *MYLIP* in lipid regulation, metabolic health, and cardiovascular risk in women.

Materials and methods

Study participants from the Trøndelag Health Study (HUNT)

The HUNT study is a large, population-based cohort study conducted in Trøndelag County, Norway. Since 1984, the study has collected questionnaire data, clinical measurements, and biological samples from ~ 229,000 participants through the four surveys HUNT1 (1984-86), HUNT2 (1995-97), HUNT3 (2006-08), and HUNT4 (2017-19)^{24,25}. Around 88,000 participants from the last three surveys have been genotyped using Illumina HumanCoreExome arrays. This data has been further imputed using the Haplotype Reference Consortium (HRC) and TOPMed imputation panels, resulting in around 33 million well-imputed variants. Genotyping and imputation procedures in HUNT are detailed in a previous publication²⁶. Sample and variant quality control were performed using standard practices described in detail elsewhere²⁷. In the present study we included all 46,071 women in HUNT who are genotyped. All participants provided written informed consent, and the study was approved by the appropriate regional ethics committee.

Exploratory analyses in HUNT

We used the HUNT study for exploratory analyses to identify diseases or phenotypes associated with genetic variation in *MYLIP*. Our analyses included a broad range of CVDs, as well as several measurements and data collected through the HUNT surveys, including female-specific variables, various blood-based biomarkers, and self-reported disease. Data on CVD outcomes were available for all participants through linkage to national health registries covering the period from 1985 to 2024. The 9th and 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10) codes derived from the Nord-Trøndelag Hospital Trust were used to construct CVD outcomes. We utilized all available data from all four HUNT surveys to maximize sample sizes. A detailed description of the phenotype data processing can be found in the

supplementary material. We analyzed all genetic variants located in or near the *MYLIP* gene, including a 50 kb region upstream and downstream of the gene. This corresponded to all variants on chromosome 6 between base pair positions 16,079,356 and 16,198,479, totaling 1,128 variants (GRCh37).

Study participants from the UKB

UKB is a large-scale, population-based biomedical cohort comprising over 500,000 participants aged 40–69 years, recruited across the United Kingdom between 2006 and 2010. All participants are genotyped using two closely related arrays: the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix and Applied Biosystems UK Biobank Axiom Array. Imputation expanded the dataset to include over 90 million genetic variants. For this study, we utilized the Genomics England (GEL) 100,000 Genomes Project–imputed dataset. Detailed protocols for genotyping, imputation, and quality control procedures have been described previously²⁸. After filtering for genetic sex, no sex chromosome aneuploidy, outliers for heterozygosity or missing rate and genetic ethnic grouping Caucasian, a total of 220,429 women were included in the analyses. Written informed consent was obtained from all participants.

Validation analyses in UKB

We used UKB data to validate findings from the exploratory analyses in HUNT. Association between *MYLIP* variants and CVD outcomes, as well as significant phenotypes identified in the HUNT, were tested in UKB. Based on the thyroid-stimulating hormone (TSH) findings in HUNT, and the hypothesis that *MYLIP* may influence hormone-related pathways, we additionally included hyperthyroidism and hypothyroidism. Some of the significant associations identified in HUNT did not have a corresponding phenotype in UKB and were therefore not tested. CVD outcomes were obtained from electronic health record linkage using ICD-10 coded hospital data. We analyzed all genetic variants located in or near the *MYLIP* gene, including a 50 kb region upstream and downstream of the gene. This corresponded to all variants on chromosome 6 between base pair positions 16,079,086 and 16,201,367, totaling 10,956 variants (GRCh38).

Statistical analysis

The genetic association analyses for binary traits were performed using SAIGE (v.1.3.1), with more detailed information in Supplementary materials. SAIGE is a generalized mixed model that accounts for sample relatedness and case-control imbalance²⁹. The continuous traits were analyzed using BOLT-LMM (v.2.3.4), a linear mixed model that accounts for population stratification and relatedness³⁰. All exploratory analyses in HUNT were adjusted for age, principal components (PCs) 1–10, and genotyping batch. The analyses of disease phenotypes based on hospital data were adjusted for birth year rather than age due to missing mortality data. All analyses in UKB were adjusted for birth year, PC1–10, and genotyping batch. A minimum minor allele frequency (MAF) of $2 \cdot 10^{-4}$ (corresponding to minimum minor allele count (MAC) of 10, 10/46,071), was applied in HUNT, and UKB analyses were restricted to variants with $\text{MAC} \geq 10$. To control for multiple testing, we applied the Benjamini–Hochberg (BH) false discovery rate (FDR) procedure with a significance threshold of 0.05. When no findings reached the significant threshold of $\text{FDR} < 0.05$, a suggestive association was applied for variants with $p < 5 \cdot 10^{-4}$. For the validation analyses of specific variants, Bonferroni correction was used to identify statistically

validated variants (0.05/number of variants tested), and a nominal threshold of 0.05 was used to indicate suggestive replication.

When comparing genetic associations between HUNT and UKB, we harmonized alleles to ensure consistent effect direction reporting. Due to differences in genotyping arrays and imputation reference panels, the same genetic variant may be reported on opposite DNA strands across cohorts. In such cases, minor allele frequencies are complementary (e.g., MAF of 0.30 in one cohort corresponds to 0.70 in the other), and effect estimates (beta coefficients) have opposite signs but represent the same biological effect. All results are reported with respect to the minor allele in the discovery cohort, with validation cohort results harmonized accordingly.

Functional annotation analyses

Functional annotation analyses were conducted to interpret the biological significance of significant SNPs identified at an FDR threshold of 0.05 in both the HUNT and UK Biobank cohorts, as well as top five most significant SNPs per disease outcome in both cohorts. The SNP locations were assessed using The Single Nucleotide Polymorphism Database (dbSNP) from NCBI, which provides curated information on variant consequence based on extensive genomic data³¹. To validate previous findings and explore potential pleiotropic effects, SNPs were cross-referenced with the GWAS Catalog, a comprehensive repository of published genome-wide association studies³². For the two missense variants, AlphaFold was used to predict the impact of amino acid substitutions on protein structure and function. The pathogenicity predictions provide insight into the implications of specific substitutions and the pLDDT score indicates confidence level for each prediction³³.

Transcription factor binding potential at SNP loci was investigated using two resources. The JASPAR CORE database offers a collection of predicted transcription factor binding profiles as position frequency matrices, which are derived from experimentally defined DNA-binding sites³⁴. Each binding site is scored quantitatively with associated p-values. We also used the ReMap Atlas of Regulatory Regions, a large-scale database aggregating ChIP-seq and other DNA-binding sequencing data³⁵. It covers over 1,200 human transcriptional regulators across 8000 datasets, including a broad range of cell types. Additional regulatory annotation resources were ORegAnno, a curated database of regulatory elements, the GeneHancer database of human enhancers and promoters, and data on cis- expression quantitative trait locus (eQTLs) from the GTEx project identified via CAVIAR, linking variants to gene expression changes^{36–38}. We also assessed candidate cis-regulatory elements (cCREs) from ENCODE³⁹.

Results

Associations with disease outcomes

No significant associations were observed between genetic variants in the *MYLIP* region and any of the 12 cardiac and metabolic diseases after correction for multiple testing in neither HUNT nor UKB. In the exploratory analyses in HUNT, a suggestive association defined as $p < 5 \cdot 10^{-4}$, was identified between *MYLIP* and self-reported hyperthyroidism (rs145657968, $p = 9.57e-05$), Fig. 1. In UKB, suggestive associations were observed between *MYLIP* and several disease outcomes, including hypothyroidism (rs1005440626, $p = 8.96e-06$), dilated cardiomyopathy (DCM; rs904384142, $p = 7.36e-06$), ischemic stroke and stroke (rs1223016952, $p = 1.47e-05$ and $p = 7.26e-05$), hypertension (rs760503257, $p = 5.92e-05$), myocardial infarction (MI; rs1759974680, $7.45e-05$),

hypertrophic cardiomyopathy (HCM; rs745594955, $p = 7.51e-05$), heart failure (HF; rs1223016952, $p = 3.3e-4$), and coronary artery disease (CAD; rs545819196, $p = 4.0e-4$), Fig. 1.

To further explore these findings, the top five single-nucleotide polymorphism (SNPs) per disease outcome in HUNT were tested for replication in UKB (Supplementary Table 1). Two SNPs were nominally validated in UKB, one SNP associated with CAD (rs192337533, $p = 0.01976$), and one SNP associated with hypertension (rs79599055, $p = 0.0305$). Conversely, of the top five SNPs per disease outcome in UKB (Supplementary Table 2), one SNP associated with hyperthyroidism was nominally validated in HUNT (rs113831599, $p = 0.0482$). It should be noted that many SNPs identified in UKB were not available in HUNT due to the smaller number of variants in HUNT compared with UKB (1,128 vs 10,956).

Association with female-specific risk factors

There was no significant association between *MYLIP*-variants and the female-specific risk factors, after correcting for multiple testing. Among the binary traits, ever having a pregnancy was the most significant trait (rs117897785, $p = 6.5e-04$). Among the continuous traits, rs143013423 showed suggestive association with menopause age ($p = 8.5e-05$) and reproductive years ($p = 1.3e-04$).

Associations with potential risk factors

In HUNT, 17 phenotypes showed significant associated with variants in the *MYLIP* region after correction for multiple testing, involving a total of 58 genetic variants (Table 1; Fig. 2, Supplementary Table 3). Of these 17 phenotypes, 11 were also available for analysis in the UKB. Among these, 10 of the 11 phenotypes, comprising 304 genetic variants, demonstrated significant associations with *MYLIP* after correction for multiple testing (Table 1; Fig. 2; supplementary Table 4).

Table 1

Phenotypes significantly associated with genetic variants in the MYLIP region after correction for multiple testing in HUNT and UKB, with the number of significant SNPs per phenotype.

Phenotype	No. of sign. SNPs HUNT	Phenotype available in UKB	No. of sign. SNPs UKB
Anti-GAD	1	no	-
TSH	8	yes	2
ASAT	3	yes	17
Troponin I	1	yes	0
Icterus	1	no	-
NRbc	1	yes	28
Mean cell hemoglobin	24	no	-
Phosphatidyl ethanol	1	no	-
Cholesterol	4	yes	91
Albumin	1	yes	1
Lymphocytes	1	yes	29
Eosinophil	1	yes	11
Triglycerides	1	yes	1
LDL-c	6	yes	111
Thyroxine (T4)	1	no	-
ALAT	2	yes	13
Vitamin K	1	no	-

Sign; significant, HUNT, Trøndelag Health Study, UKB; UK Biobank; Anti-GAD; anti-glutamic acid decarboxylase, TSH; Thyroid-Stimulating Hormone, ASAT; aspartate aminotransferase, NRbc; Nucleated Red Blood cells, LDL-c; Low density lipoprotein cholesterol, ALAT; alanine aminotransferase.

Among the 58 significant SNPs identified in HUNT, 10 were significantly associated with the same phenotype in UKB after applying a Bonferroni correction threshold ($p < 0.00086$; $0.05/58$), with effect directions harmonized to account for potential strand differences between cohorts. These validated SNPs were associated with LDL-c (6 SNPs) and total cholesterol (4 SNPs). As four SNPs overlapped across the two phenotypes, a total of six unique SNPs were validated in UKB (Table 2).

Table 2

Information about the significant SNPs from HUNT that were validated in UKB. Beta coefficients are aligned to the minor allele in the discovery cohort. Complementary MAF values (e.g., 0.30 vs 0.70) reflect opposite strand reporting. More details of the SNPs are in Supplementary Table 3.

SNP ID	MAF (HUNT)	BETA (HUNT)	Pheno	p-val (HUNT)	p-val BH (HUNT)	MAF (UKB)	BETA (UKB)	p-val (UKB)	MYLIP Location
rs7746081	0.3171	-0.0374	Chol	3.5e-06	0.0158	0.6985	0.0315	4.5e-18	
rs7746081	0.3171	-0.0356	LDL-c	4.3e-06	0.0176	0.6997	0.0145	1.4e-14	
rs6459450	0.3205	-0.0366	Chol	5.2e-06	0.0176	0.6956	0.0318	1.6e-18	
rs2235215	0.3185	-0.0366	Chol	5.2e-06	0.0176	0.6982	0.0316	3.4e-18	intron
rs2235215	0.3185	-0.0348	LDL-c	7e-06	0.0216	0.6994	0.0145	1.5e-14	Intron
rs6459450	0.3205	-0.0348	LDL-c	7.6e-06	0.0223	0.6969	0.0145	1.3e-14	
rs1569447	0.3132	-0.0314	LDL-c	3.4e-05	0.0469	0.7145	0.0135	1.9e-12	
rs3757354	0.2226	-0.0345	LDL-c	3.9e-05	0.0469	0.7988	0.0119	3.4e-08	2KB upstream variant
rs760633	0.2226	-0.0344	LDL-c	4e-05	0.0469	0.7990	0.0121	2.3e-08	2KB upstream variant
rs1569447	0.3132	-0.0320	Chol	4.7e-05	0.0484	0.7136	0.0298	6.6e-16	

MAF; Minor allele frequency, HUNT; The Trøndelag Health Study, pheno; phenotype, p-val; p-value, BH; Benjamini Hochberg, UKB; UK Biobank, Chol; cholesterol, LDL-c; Low density lipoprotein cholesterol, KB; kilobase pair.

Conversely, among the 304 *MYLIP* SNPs identified to be associated with the continuous phenotypes in UKB, 13 were significantly associated with the same phenotype in HUNT after Bonferroni correction ($p < 0.00016$; $0.05/304$). These validated variants were associated with LDL-c (6 SNPs) and total cholesterol (7 SNPs), with six SNPs overlapping across the two traits, resulting in seven unique validated variants. This included one additional SNP (rs9464867) that was not among the significant variants originally identified in HUNT. Furthermore, nominal replication ($p < 0.05$) was observed for LDL-c (62 SNPs) and total cholesterol (74 SNPs), whereas 60 of the SNPs overlapped between LDL-c and total cholesterol.

Cross-phenotype validation analyses

Cross-trait validation analyses were also performed. The top 10 SNPs associated with LDL-c, total cholesterol, and triglycerides in HUNT were examined for associations with the CVD outcomes that are affected by lipid-traits; CAD, MI, and hypertension in UKB (Supplementary Table 5). One SNP associated with LDL-c in HUNT was

nominally validated for hypertension in UKB (rs2294266, $p = 0.0195$), and one SNP associated with triglycerides in HUNT was nominally validated for MI in UKB (rs11750953, $p = 0.0457$). Furthermore, the eight SNPs that were significantly associated with TSH in HUNT were evaluated for associations with self-reported hyperthyroidism or hypothyroidism in HUNT, and TSH, hyperthyroidism, and hypothyroidism in UKB (Supplementary Table 6). Five of the eight SNPs were nominally associated with self-reported hypothyroidism in HUNT, but no associations were found in UKB.

Functional annotation of associated variants

We performed functional annotation analyses of all SNPs significantly associated with risk factors in HUNT and UKB after correction for multiple testing, as well as the five most significant SNPs per disease outcome. The analysis revealed several regulatory regions, including transcription factor binding sites, enhancer elements, promoters, and eQTLs, as well as two missense variants (Supplementary Tables 7–10). The missense variant rs199758517 was associated with ASAT and ALAT levels, and rs9370867 with LDL-c and total cholesterol. Using AlphaFold, both variants showed low pathogenicity scores (0.098 for rs199758517 and 0.144 for rs9370867), classifying them as likely benign. The corresponding model confidence scores (pLDDT) were 91 for rs199758517, indicating very high confidence, and 45 for rs9370867, indicating low structural confidence.

Our analysis further identified eQTLs influencing *MYLIP* expression across multiple tissues, including skeletal muscle, thyroid, and brain (rs531490250, rs571101237, rs6920309, rs907731996 and rs541565430). These were SNPs associated with ASAT, ALAT, cholesterol, LDL-c and stroke. Among the 124 unique SNPs associated with total cholesterol and/or LDL-c in HUNT and UKB, 48 had been previously reported in association with lipid-related traits. Several of these lipid-associated SNPs were located in regulatory regions: for example, rs6920309 maps to a predicted binding site for the PPAR γ –RXR α heterodimer ($p = 10^{-4}$), and rs6459452 to a predicted binding site for HNF4A, based on ORegAnno and ReMap data.

Regulatory regions were also identified for SNPs associated with hematological traits. The variant rs6905841, associated with mean corpuscular hemoglobin, was located in predicted binding sites for GATA2 and GATA3, members of the hematopoietic GATA transcription factor family. Four variants associated with eosinophil or lymphocyte counts (rs1156579586, rs1043733300, rs562765522, and rs776863888) overlapped transcription factor binding sites in lymphocytes and leukemia cell lines, according to ReMap. Notably, the lymphocyte-associated variant rs562765522 was located within a predicted SPI1 binding site, also supported by JASPAR predictions ($p = 10^{-5}$).

Among the top disease-associated variants, several SNPs were located within binding sites of factors previously implicated in CVD. The HCM-associated SNP rs17581000 mapped to a FOXO1 binding site, while rs772860028 overlapped predicted binding sites for Krüppel-like factors (KLF2, KLF12, KLF15). Two SNPs associated with non-ischemic stroke (rs996424586 and rs778558279) localized to predicted binding sites of CREB3, CREB3L2, CREB3L1, CREB3L4, and SMAD3. All binding site predictions were derived from JASPAR ($p = 10^{-4}$). Using ReMap, we further identified variants within ERG binding sites in arterial endothelial cells, including rs1338670550 and rs1465872898 (associated with hyperthyroidism), rs973085432 (MI), rs964003395 (HF), and rs141520926 (TSH).

Table 3

Information about the missense variants identified in UKB. Beta coefficients are aligned to the minor allele in the discovery cohort. Complementary MAF values (e.g., 0.30 vs 0.70) reflect opposite strand reporting.

SNP ID	MAF UKB	BETA UKB	p-val UKB	Pheno	FDR	MAF HUNT	BETA HUNT	p-val HUNT	MYLIP location
rs199758517	0.999935	-27.187	5.8e-20	ALAT	9.11e-17				Missense Variant
rs199758517	0.999934	-15.181	5.4e-11	ASAT	2.22e-08				Missense Variant
rs9370867	0.538664	0.0259	7e-15	Chol	4.89e-12	0.4692	-0.0211	0.0041	Missense Variant
rs9370867	0.538544	0.0114	4.4e-11	LDL-c	1.84e-08	0.4692	-0.0222	0.0014	Missense Variant

SNP; single-nucleotide polymorphism, MAF; Minor allele frequency, UKB; UK Biobank, p-val; p-value, pheno; phenotype, FDR; false discovery rate, HUNT; The Trøndelag Health Study, ALAT; alanine aminotransferase. ASAT; aspartate aminotransferase, Chol; cholesterol, LDL-c; Low density lipoprotein cholesterol.

Discussion

In this study, we investigated associations between genetic variants in or near the *MYLIP* gene and a broad spectrum of cardiovascular and metabolic disease outcomes, risk factors, and female-specific factors in women, using data from HUNT and UKB. Our results showed no statistically significant associations between *MYLIP*-proximal variants and disease outcomes after correction for multiple testing, although several suggestive associations were observed for hypothyroidism, DCM, ischemic stroke, HCM, MI, hypertension, HF, and CAD. None of the female-specific risk factors were significant after correction for multiple testing, but menopause age and reproductive years demonstrated suggestive associations. In contrast, several risk factor phenotypes, particularly lipid, blood, hormone, and liver-related traits, were significantly associated with variants in the *MYLIP* region in both cohorts. Of these, associations with LDL-c and total cholesterol were robustly replicated across studies, underscoring the central role of *MYLIP* in lipid metabolism in women. Our findings confirm the established role of *MYLIP* in lipid regulation and reveal novel associations with thyroid and liver traits, while showing limited evidence for direct associations with several CVD endpoints.

The well-established relationship between *MYLIP* and lipid traits, especially LDL-c, total cholesterol, and triglycerides, was confirmed in this female-only analysis. These findings suggest that *MYLIP* contributes to lipid regulation in women, consistent with prior functional and genetic studies in mixed populations. Interestingly, despite these strong lipid associations, we observed no statistically significant associations between *MYLIP* variants and CAD, MI, or hypertension in either HUNT or UKB, after correction for multiple testing. This is noteworthy given that elevated LDL-c and triglycerides are well-established causal risk factors for CVD, with extensive epidemiological and genetic evidence supporting their role in atherosclerosis and CVD pathogenesis. The absence of detectable CVD associations despite clear lipid effects may reflect limited statistical power to detect associations with binary disease outcomes compared with continuous metabolic traits. Alternatively, the effect of *MYLIP* on lipid levels, while statistically robust, may be too modest in magnitude to translate into measurable differences in clinical CVD endpoints. The effect size for the genetic variants associated with LDL-c

and cholesterol is ~ 0.03–0.04 mg/dL, which is less than normal daily fluctuation ⁴⁰. It is therefore likely that each genetic variant alone will not affect lipid-levels enough to cause CVD, but the combined effect of multiple genetic variants might be sufficient. It is also possible that *MYLIP*'s influence on cardiovascular risk depends on additional factors, such as lipid particle composition, metabolic context, or interactions with other genetic or environmental modifiers not captured in our analysis. Nonetheless, the suggestive associations with MI, CAD, and hypertension observed here, in combination with nominal validation of one LDL-c SNP in hypertension and one triglyceride SNP in MI across the cohorts, indicate that *MYLIP* may still exert subtle or context-dependent effects on cardiovascular risk that warrant further investigation in larger studies. Functional annotation of lipid-associated variants suggested potential regulatory mechanisms linking these SNPs to lipid metabolism. The variant rs6920309 was located within a predicted binding site for the PPAR γ –RXR α heterodimer (peroxisome proliferator-activated receptor gamma and retinoid X receptor alpha), a key transcriptional complex regulating lipid metabolic pathways⁴¹. Another variant, rs6459452, was located within a predicted binding site for HNF4A (hepatocyte nuclear factor 4 alpha), a transcription factor central to hepatic lipid metabolism ⁴².

The missense variant associated with LDL-c and cholesterol in UKB, rs9370867, has been associated with hyperlipidemia in a Chinese Han cohort and with LDL-c uptake and circulating cholesterol in a Mexican population ^{43,44}. In contrast, no significant associations were reported in Brazilian, Dutch or Italian populations ^{6,45,46}. The allele distribution of rs9370867 appears to vary across populations, and in the British cohort examined here, it is associated with cholesterol levels. rs9370867 results in an asparagine-to-serine substitution at position 342 (N342S), and the study on the Mexican population showed that this could be a beneficial substitution associated with lower circulating LDL-cholesterol levels ⁵. The low pathogenicity score from our AlphaFold analyses indicated that the amino acid change is likely benign, meaning it is unlikely to affect protein structure. rs9370867 lies in the functional FERM-domain of *MYLIP*, and Weissglas-Volkov and colleagues showed that the substitution was critical for LDLR targeting thereby affecting LDL-cholesterol levels, but that it did not affect *MYLIP* E3 ligase activity. Taken together, this suggests that the substitution may alter local interactions at the LDLR binding interface, modulating protein function through target recognition rather than by changing overall protein folding or stability.

One of the SNPs with a well-established association to lipid traits, both in our study and other GWAS, rs3757354, has also been linked to aerobic fitness and metabolic traits in women specifically, and later also early-onset preeclampsia^{13,47}. This shows how genetic variation in *MYLIP* influencing lipid metabolism or other biological processes may contribute to disease pathophysiology in women. In a candidate gene study focused on CAD, an association between rs3757354 and increased risk of CAD was reported, and well as response to lipid-lowering therapy in the form of carotid intima-media thickness regression and changes in plasma lipids ⁴⁸, thus providing a more direct link to CVD.

Functional annotation of the top SNPs associated with cardiovascular outcomes revealed variants located in regulatory regions relevant to cardiac and vascular function, potentially strengthening the proposed link between *MYLIP* and cardiovascular disease risk. An HCM-associated SNP was identified within a FOXO1 binding site and given FOXO1's high cardiac expression and established role in hypertrophy, altered binding could contribute to pathological remodeling ⁴⁹. Another HCM-related SNP overlapped predicted binding sites for Krüppel-like factors, key regulators of cardiac remodeling and hypertrophy ^{50,51}. SNPs associated with non-ischemic stroke were mapped to CREB3 and SMAD3 binding sites. CREB3 proteins influence metabolic and atherosclerotic pathways,

while SMAD3, a mediator of TGF- β signaling, is upregulated after stroke in experimental models^{52,53}. Additionally, variants related to metabolic or cardiac disease were located within predicted ERG binding sites in arterial endothelial cells. Given ERG's essential role in maintaining endothelial identity and vascular homeostasis and recent link to inflammation and atherosclerosis^{6,47}, these findings may suggest that disruption of ERG binding due to this *MYLIP* SNP may contribute to endothelial dysfunction and heightened CVD risk.

A novel and noteworthy finding was the association between *MYLIP* variants and thyroid-related traits. Variants in *MYLIP* were significantly associated with serum TSH levels in both HUNT and UKB after correction for multiple testing. Elevated TSH has been shown to influence lipid metabolism, with higher TSH levels linked to less favorable lipid profiles⁵⁴. The additional association between *MYLIP* and thyroxine (T4) in HUNT further supports a role for *MYLIP* in thyroid hormone regulation in women. However, thyroxine levels were unavailable in UKB, precluding replication. Notably, a recent study from our group identified TSH as a major risk factor for myocardial infarction and CVD mortality in women, but not in men, suggesting that the interplay between *MYLIP*, thyroid function, and cardiovascular risk may be sex-specific⁵⁵. In line with this, we also observed suggestive associations between *MYLIP* and both hyperthyroidism and hypothyroidism, although these did not reach significance after correcting multiple testing. Furthermore, five out of the eight SNPs that were significantly associated with TSH in HUNT were nominally validated in self-reported hypothyroidism in HUNT, strengthening the link between *MYLIP* and thyroid hormone regulation in women. These findings could possibly reflect that individuals with hyperthyroidism or hypothyroidism have lower or higher cholesterol-levels, respectively. Lastly, while we observed some associations between *MYLIP* variants and reproductive traits including pregnancy history and age at menopause, these did not survive multiple testing correction and warrant further investigation in larger cohorts.

We identified an intronic *MYLIP* variant associated with troponin I levels in HUNT; however, this association was not replicated in UKB. The lack of replication may reflect methodological differences, as troponin I was measured by gold-standard clinical measurements in HUNT, and by non-clinical proteomic assays in UKB. Despite this, the finding warrants further investigation given troponin I's established role as a biomarker of subclinical MI. Additionally, ASAT, an enzyme present in liver, heart, and muscle tissue, was significantly associated with *MYLIP* in both HUNT and UKB, with 17 variants FDR significant in UKB. Elevated ASAT is linked to metabolic stress, myocardial infarction, and metabolic syndrome⁵⁶. Notably, 9 of the 17 ASAT-associated variants showed no overlap with liver-specific markers (ALAT or albumin), potentially reflecting *MYLIP*'s influence specifically in cardiac or skeletal muscle tissue where ASAT is also expressed, which may be relevant for understanding cardiovascular risk independent of hepatic metabolism.

In addition to ASAT, liver-specific markers including ALAT and albumin were significantly associated with *MYLIP* variants in both cohorts. ALAT is elevated in metabolic syndrome, obesity, and insulin resistance, and is associated with increased CVD risk⁵⁷. Albumin, the most abundant plasma protein produced by the liver, plays a key role in transporting hormones and circulating molecules. Low serum albumin indicates chronic inflammation and has been linked to adverse cardiovascular outcomes⁵⁸. Among the 13 SNPs associated with ALAT, 8 overlapped with ASAT, likely representing a core hepatic signal affecting general hepatocellular function. The albumin SNP did not overlap with ALAT nor ASAT.

Strikingly, variants associated with hepatic markers (ALAT, ASAT, and albumin) were independent from lipid trait associations. Across all 23 hepatic-associated variants, none were overlapping or were in linkage disequilibrium

(LD) with the 119 lipid-associated variants, representing genomic separation. This was unexpected, as we initially hypothesized that liver enzyme associations would reflect metabolic consequences of altered hepatic lipid handling, given *MYLIP*'s established role as a regulator of LDLR degradation. However, the genomic independence indicates that *MYLIP* influences liver enzymes and protein synthesis through regulatory regions distinct from those controlling lipid metabolism, potentially involving separate effects on hepatocellular integrity, inflammatory signaling, or tissue-specific expression. This functional pleiotropy may help explain why *MYLIP*'s robust lipid associations do not translate proportionally into clinical CVD outcomes, as non-lipid pathways may exert context-dependent influences on cardiovascular risk not captured by lipid measurements alone.

We also observed significant associations between *MYLIP* variants and immune-related hematological traits, specifically lymphocyte and eosinophil counts, in both HUNT and UKB. These white blood cell types are central to inflammatory and metabolic regulation, and lower levels of either have been linked to increased short-term risk of heart failure and coronary death in the general population ⁵⁹. Moreover, nucleated red blood cells (NRBCs) were significantly associated with *MYLIP* in both cohorts. NRBCs are normally restricted to the bone marrow, and their presence in peripheral blood indicates hypoxia, bone marrow stress or severe illness ⁶⁰. Circulating NRBCs has been linked to higher mortality risk and adverse cardiovascular outcomes ⁶¹. Functional annotation analysis revealed that several of the SNPs associated with hematological traits fall in predicted binding sites for factors that are central regulators of hematopoiesis and immune cell function, such as GATA2 and GATA3, which are critical for the development and maintenance of blood cells and SPI1, which is a vital regulator of immune cell differentiation ^{62 63}. Taken together, these consistent hematological associations suggest that *MYLIP* may influence cardiometabolic health not only through liver and hormonal pathways but also through immune and stress-response mechanisms relevant to cardiovascular disease.

Several phenotypes associated with *MYLIP* in HUNT lacked corresponding measures in UKB, including anti-glutamic acid decarboxylase (anti-GAD) antibodies, mean cell hemoglobin (MCH), phosphatidyl ethanol (PEth), Icterus index, Thyroxine, and vitamin K. Although their links to *MYLIP* require further validation, each trait has potential relevance to cardiometabolic or hormonal pathways. Anti-GAD antibodies reflect autoimmune processes, and notably, one study reported nearly a fourfold increased risk of myocardial infarction in women positive for anti-GAD, with no excess risk observed in men ⁶⁴. MCH is the average amount of hemoglobin per red blood cell and is critical for oxygen transport. Several studies have suggested a U-shaped association between hemoglobin and CVD risk in men, while women are suggested to have a linear increased CVD risk with higher hemoglobin levels ^{65,66}. PEth, a biomarker of chronic alcohol intake, is linked to increased risk of various cardiovascular problems including arrhythmia, cardiomyopathy, hypertension, MI, and stroke. Furthermore, alcohol intake damages the liver, potentially explaining the association between Peth and genetic variants in *MYLIP*. The icterus index reflects bilirubin accumulation and may indicate hepatic dysfunction relevant to metabolic health. Lastly, Vitamin K is essential for the liver to produce coagulation factors and for vascular health. Higher dietary intake of vitamin K is associated with lower risk of atherosclerotic CVD as vitamin K helps regulate calcium, prevent vascular calcification, reduces arterial stiffness and blood pressure ⁶⁷. Together, these unvalidated findings highlight additional potential connections between *MYLIP* and cardiometabolic or hormone-related processes that warrant future investigation.

Several limitations should be considered when interpreting these findings. First, phenotype definitions differed between cohorts for some traits, which may have affected cross-cohort validation. Disease outcomes (hypothyroidism and hyperthyroidism) were ascertained through ICD-coded hospital registry data in UKB but

relied on self-reported questionnaire data in HUNT. Similarly, troponin I measurements were derived from non-fasting serum samples in HUNT, whereas UKB employed Olink proteomics technology. These methodological differences may explain some discrepancies in validation results.

Second, our analytical approach involved testing a large number of genetic variants without linkage disequilibrium (LD) pruning, given the exploratory nature of the study and the compact genomic architecture of the *MYLIP* locus. Consequently, many tested SNPs are in high LD and therefore not statistically independent. While we applied false discovery rate correction to control for multiple testing, this approach may be overly conservative given the non-independence of tests. To balance Type I and Type II error rates, we reported suggestive associations ($p < 5 \times 10^{-4}$) for disease outcomes, though these require validation in independent datasets.

Third, our study was conducted exclusively in women of European ancestry from two Northern European populations (Norway and the United Kingdom). While this design strengthens our ability to detect female-specific effects and minimizes confounding from population stratification, it limits the generalizability of our findings to men, to women of non-European ancestry, and to populations with different genetic architectures or environmental exposures.

Lastly, our study is observational and based on genetic associations, which precludes direct inference about causality or underlying biological mechanisms. Functional studies are needed to elucidate the molecular mechanisms linking *MYLIP* variants to the observed phenotypic associations, particularly for the novel thyroid and liver-related findings.

Conclusions

In summary, our study provides evidence that genetic variation in the *MYLIP* region is strongly associated with multiple cardiometabolic risk factors, particularly lipid- and liver-related traits, in women. The robust associations with LDL-c and total cholesterol confirm the central role of *MYLIP* in lipid regulation, while the novel associations with thyroid- and liver-related traits suggest broader metabolic functions. Although we did not observe statistically significant associations with CVD endpoints, the consistent direction and suggestive nature of several findings support *MYLIP* as a pleiotropic gene influencing metabolic health in women. Future work should explore potential mechanistic links between *MYLIP*, thyroid function, lipid metabolism, and cardiovascular disease, ideally in sex-stratified and functional studies.

Declarations

Competing interests

The author(s) declare no competing interests.

Ethics declarations

This study was approved by the Regional committee for medical research ethics (2019/29771), the Trøndelag Health Study, the Norwegian Data Inspectorate, and by the National Directorate of Health. The study is in

conformity with Norwegian laws and the Helsinki Declaration. The UKB research protocol and study design were approved by the NHS National Research Ethics Service (Project ID 40135). Ethical approval was obtained from the Northwest Centre for Research Ethics Committee (MREC, 11/NW/0382). In Scotland, the UKB has approval from the Community Health Index Advisory Group (CHIAG).

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Author Contribution

Conceptualization: A.N.N., M.K., A.B.; Formal analysis: A.N.N., M.K.; Software: A.N.N., M.K.; Visualization: A.N.N., M.K.; Writing—original draft preparation: A.N.N., M.K.; Writing—review and editing: A.N.N., M.K., G.K., A.B.; Supervision: A.B.; A.N.N. and M.K. contributed equally to this study.

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Data Availability

Researchers affiliated to a Norwegian research institution can apply for HUNT data access from HUNT Research Centre (www.ntnu.edu/hunt) if they have obtained project approval from the Regional Committee for Medical and

Health Research Ethics (REC). Researchers not affiliated to a Norwegian research institution should collaborate with and apply through a Norwegian principal investigator. Information on the application and conditions for data access is available at www.ntnu.edu/hunt/data. The HUNT Databank website provides a detailed overview of the available variables in HUNT (www.ntnu.edu/hunt/databank). Certain data from ancillary HUNT projects may be subject to a time-limited exclusivity provided to the researchers who have financed and conducted the data collection. Biologic material is available for analyses, information on procedures is found at the HUNT Biobank website (<https://www.ntnu.edu/hunt/hunt-biobank>). Data from the health registries are not kept by HUNT; instead, linkages between HUNT and registry data have to be made for each research project and require that the principal investigator has obtained project-specific approval for such linkage by REC and each registry owner.

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Figures

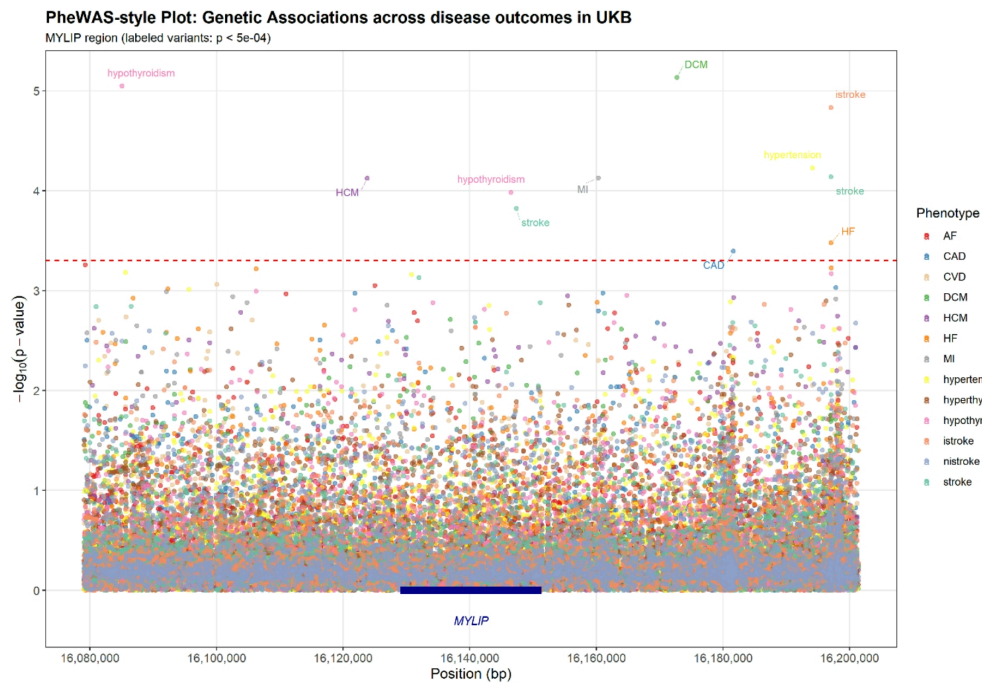
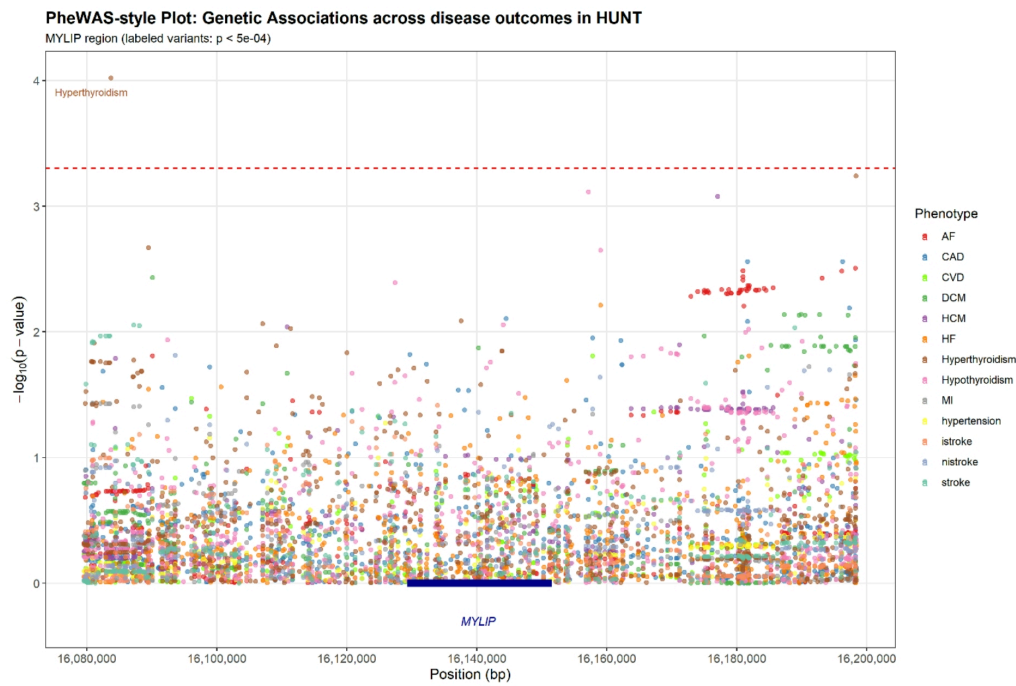
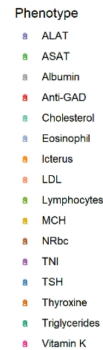


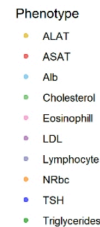
Figure 1

Regional association plots for the MYLIP locus showing suggestive associations with disease outcomes in HUNT (top) and UKB (bottom). The x-axis represents the genomic position on chromosome 6, and the y-axis represents the $-\log_{10}(p)$ value. The red dashed line indicates a suggestive significance threshold of $p = 5 \times 10^{-4}$; variants above this line indicate suggestive evidence of association.

MYLIP region (labeled variants: FDR < 0.05)



MYLIP region (Red dotted line: FDR < 0.05)



Regional association plots for the MYLIP locus showing suggestive associations with disease outcomes in HUNT (top) and UKB (bottom). The x-axis represents the genomic position on chromosome 6, and the y-axis represents the $-\log_{10}(p)$ value. The red dashed line indicates a suggestive significance threshold of $p = 5 \times 10^{-4}$; variants above this line indicate suggestive evidence of association.

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