



HAL
open science

Exhaustive Identification of Pleiotropic Loci for Serum Leptin Levels in the NHGRI-EBI Genome-Wide Association Catalog

Anthony Haidamous, David Meyre, Sébastien Hergalant

► To cite this version:

Anthony Haidamous, David Meyre, Sébastien Hergalant. Exhaustive Identification of Pleiotropic Loci for Serum Leptin Levels in the NHGRI-EBI Genome-Wide Association Catalog. Journées Ouvertes en Biologie, Informatique et Mathématiques, Société Française de Bioinformatique, Jul 2025, Bordeaux, France. pp.231. <hal-05219695>

HAL Id: hal-05219695

<https://hal.univ-lorraine.fr/hal-05219695v1>

Submitted on 22 Aug 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Exhaustive Identification of Pleiotropic Loci for Serum Leptin Levels in the NHGRI-EBI Genome-Wide Association Catalog

Anthony HAIDAMOUS¹, David MEYRE^{1,2}, Sébastien HERGALANT¹

1 INSERM U1256, NGERE, Université de Lorraine, 54000, Nancy, France

2 Service de Biochimie et Biologie Moléculaire, CHRU de Nancy, 54000, Nancy, France

Corresponding author: sebastien.hergalant@univ-lorraine.fr

Keywords

Leptin, Genome-wide associations studies, Gene pleiotropy, Variant effect, Protein-protein interaction modules.

Abstract

Leptin is an adipokine that regulates energy expenditure and calory intake by acting on the hypothalamic leptin-melanocortin pathway. It has known effects on obesity, inflammation, and neurodevelopment, hence carrying high pleiotropic potential. Using the Genome-Wide Association Study (GWAS) Catalog, we identified the single nucleotide polymorphisms (SNPs) associated with fluctuations of leptin in the blood, which we expanded into wider genetic blocks, and explored their associations and effect sizes with leptin levels. We then investigated the genetic pleiotropy linked with these genomic regions.

Starting from 35 GWAS studies on leptin levels with a minimum discovery sample size > 1000 individuals, we selected 25 SNPs reaching genome-wide significance ($p < 5.10^{-8}$). This led to the aggregation of 15 genetic blocks with SNPs in high linkage disequilibrium with the leptin SNPs. The blocks were also associated with 574 pleiotropic phenotypes, which were then grouped into 22 categories, including the enriched “other adipokines” ($n=3$, fold-enrichment against background: $e=3.5$, effects in reverse directions with leptin), “obesity-related” ($n=11$, $e=15$, increasing with leptin), “inflammation-related” ($n=47$, $e=2$), “cancer-related” ($n=12$, $e=1.7$, effects in reverse directions with leptin), “body fat” ($n=33$, $e=2.3$, increasing with leptin), “type-2-diabetes-related” ($n=107$, $e=1.6$), and “addiction-related” ($n=61$, $e=2.3$) cross-traits. The list of genes overlapping with the genetic blocks was used to map a protein-protein interaction network surrounding leptin with which we identified functional modules enriched in ontological terms such as the leptin-melanocortin pathway, embryogenesis, immunity and transcription regulation.

This study extends the genetic architecture behind leptin levels to its wider roles in human physiology by deciphering molecular pathways and gene modules implicated in its end effects.

Introduction

Obesity is a pandemic that affects more than 38% of the global population (World Obesity Atlas 2023 report). It is defined as an abnormal accumulation of body fat and is associated with complexities and morbid diseases, such as type 2 diabetes (T2D) (1,2), cardiovascular diseases (3) and cancers (4–7). A key player in the pathophysiology of obesity is leptin, a small adipokine produced from the *LEP* gene (8) almost exclusively by the adipose tissue, and released in the serum after energy intake (9,10). Leptin acts primarily in the hypothalamus to activate neuroendocrine pathways that will insure its main functions of satiety and lipid metabolism control (11). In order to understand the factors that affect serum leptin levels and decipher the pleiotropic effects surrounding its physiological expression, we developed a method that exhaustively identifies all the leptin-associated single nucleotide polymorphisms (SNPs) reported by Genome-wide associations studies (GWAS) and infers genotype-phenotype correlations (12) between leptin and a number of related traits, such as obesity (13,14), T2D and insulin levels (14,15), cardiovascular diseases (16), and inflammation (2). Among these associations, some involve pleiotropic genes, *i.e.* influencing multiple functions and/or multiple phenotypes. Current GWAS and pleiotropy analyses can identify associations among traits and variants but lack the resolution to untangle the links between groups of genetic variants and causal genes as well as biological pathways. The original approach presented in this study calculates genetic blocks of linkage disequilibrium SNPs aggregated from the GWAS leptin loci and extracts cross-phenotypes associations, effect sizes and directions as compared to leptin. It then identifies protein-coding genes within these genomic regions and maps out their pleiotropic potential using a functional enrichment method based on protein-protein interactions, method that also infers new genes associated with leptin while excluding non-interacting genes.

Methods

Genome-wide association studies catalog. The NHGRI-EBI Catalog of Published Genome-Wide Association Studies (GWAS Catalog) (17), up to date from March 11th, 2024, and annotated for the GRCh38/hg38 human reference genome, was used extensively during this study.

R and its packages. GWAS Catalog data were downloaded for local use, handled, and manipulated using R4.3.2 (18). Key packages such as ggplot2 (used for graphs and data visualization), dplyr (used for data cleaning), karyotploteR (19) (used for blocks and genes visualization on chromosomes), and LDlinkR (20) (used for linkage disequilibrium analysis) were used.

LDlink. Within the LDlink suite (<https://ldlink.nih.gov/?tab=home>, February 7th, 2024) (21), LDproxy is a tool allowing for an exploration of proxy variants associated with an input query SNP. We used GWAS

leptin-associated SNPs as query/lead SNPs (ISNPs) for the calculations, with the 1000 genome project data as reference. Leptin ISNPs were defined as reaching genome-wide significance ($p < 5.10^{-8}$) in a study using a minimum discovery sample size > 1000 individuals. LDproxy outputs report variants associated to each ISNP ranked by their LD correlation value (r^2) in their respective populations, encoded by ethnicity (EUR: European, AFR: African, AMR: Ad-mixed Americans, EAS: East-Asians, SAS: South Asians) according to the discovery cohorts of the ISNP.

Genetic blocks, variants, and cross-traits. Using the ISNP ($r^2 = 1$), proxy SNPs (pSNPs) ($r^2 \geq 0.9$), and non-independent SNPs ($r^2 \geq 0.1$), genetic blocks of LD were aggregated. If multiple ISNPs were mapped to the same block, we retained a main lead variant as the one with the smallest association p-value. Block ethnicities were assigned based on combined ethnicities for the lead SNPs. Using every ISNPs + pSNPs, we compiled a table of cross-traits (phenotypes/traits/diseases also associated with the variants, but not leptin, $p < 5e-8$), which was hierarchized into general traits used to form categories of traits.

Fold-enrichment analyses were conducted for traits and categories, giving insight on their representation and distribution within the leptin blocks as compared to what is expected from the background. Enrichments were calculated following the relation: frequency of the observed trait / expected frequency, where the observed frequency represents the number of reported occurrences for the trait in the leptin selection among the total number of reported leptin cross-trait occurrences, and the expected frequency represents the overall significant occurrences for the same trait among the total number of significant associations in the complete GWAS Catalog ($p < 5e-8$). Two-way Fisher's exact test was used to evaluate the enrichment statistical significance ($p < 0.05$).

Gene-based functional annotations and pleiotropic networks. Using the list of protein coding genes overlapping with the genetic blocks of LD and reported as "mapped genes" with each ISNPs, we formed a network of significantly enriched protein-protein interactions (PPI, enrichment p-value $1e-05$) with STRING-db (<https://string-db.org/>), a repository of functional and physical PPI data (22,23). The generated network was then augmented with first-shell interactors ($n =$ same number as input genes) with a confidence score of 0.5, and clustered using the k-means algorithm for functional module identification. Each cluster was subject to functional annotations using the databases found in EnrichR (24–26) for pathway (Reactome, KEGG, BioPlanet and BioCarta), ontology (GO biological process, cellular component, and molecular function), and disease (PhenGenI) enrichment. Each cluster was then isolated and augmented with 10 additional first-shell interactors for further characterization (workflow in **Figure 1**).

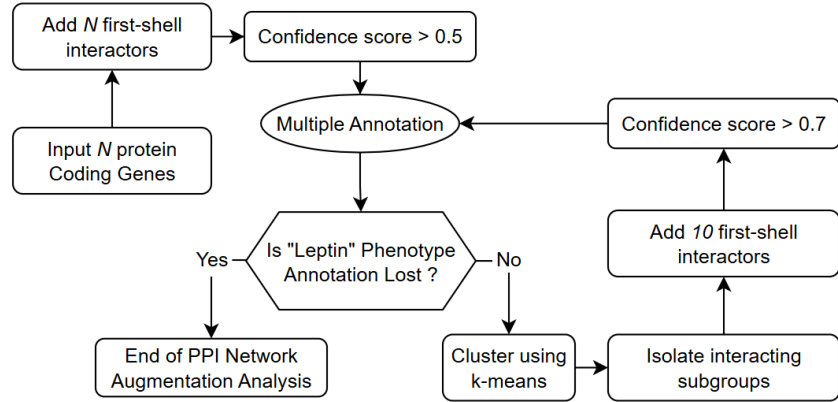


Figure 1. Flowchart describing the algorithm used for constructing and annotating the pleiotropic network around Leptin.

Results

Leptin genetic pleiotropy. Upon selecting significant SNPs mapped to “leptin measurement” and “BMI-adjusted leptin measurement” in the GWAS Catalog (discovery cohort > 1000 individuals; p-value < 5e-8), we obtained a list of 25 lead leptin SNPs (ISNPs) (Figure 2A). The list was then used for the LD analysis, which resulted in 343 proxy SNPs (pSNPs; $r^2 \geq 0.9$) and 3714 non-independent SNP ($r^2 \geq 0.1$). All variants were aggregated under their ISNPs into 15 genetic blocks of highly correlated structure (Figure 2B-C). Main characteristics for the genetic block constitution is summarized in Table 1.

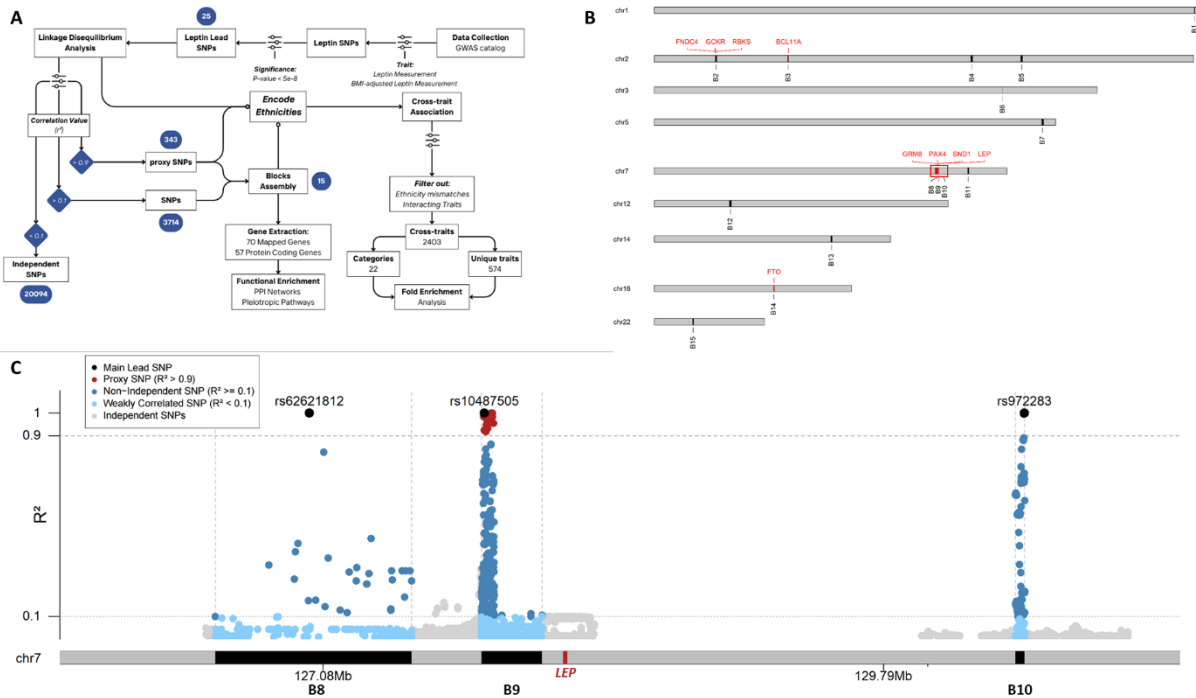


Figure 2. Workflow and Genetic Blocks. (A) Flowchart illustrating the step-by-step extraction of adiponectin SNPs and cross-trait associations, (B) Overview of the blocks' positions on the human chromosomes, red box shows blocks in proximity to the LEP gene, and (C) Close-up on the blocks' structures and LD SNPs delimited by the red box in (B).

Block	Block span (kb)	Number of ISNPs	Number of pSNPs	Number of SNPs	Number of cross-traits	Number of overlapping genes	Ethnicities
B1	353	2	16	254	0	2	AFR
B2	819	2	3	525	1481	16	EUR, AFR, EAS, AMR
B3	478	1	0	100	0	1	AFR
B4	946	1	10	112	0	2	AFR
B5	852	1	11	356	295	5	EUR, AFR, EAS, AMR
B6	138	2	16	52	138	1	EUR, AFR, EAS, AMR
B7	961	1	0	37	0	3	AFR
B8	949	1	0	27	0	7	EUR, AFR, EAS, AMR
B9	730	5	12	137	6	10	EUR
B10	45	1	1	111	2	1	EUR
B11	570	2	42	297	3	5	AFR
B12	987	1	14	625	0	1	AFR
B13	766	1	0	77	0	1	AFR
B14	75	3	85	170	478	1	EUR
B15	495	1	1	7	0	5	AFR

Table 1. Leptin genetic bloc characteristics. See Methods for ethnicity encodings.

Cross-trait analysis. Using the list of ISNPs + pSNPs, we associated 574 pleiotropic phenotypes (or cross-traits) within these blocks, which we categorized into 22 main items. The cross-trait occurrences were checked for over-representation against background (the entire significant GWAS Catalog associations), which uncovered a number of significantly enriched categories containing traits related to “diet or taste” (fold-enrichment $e = 4.4$), “other adipokines” ($e = 3.5$), “addiction” ($e = 2.4$), “body fat” ($e = 2.3$), “inflammation” ($e = 2$), “lipids” ($e = 1.7$) and “cancer-related” ($e = 1.7$), as well as some depleted categories related to “brain” ($e = 0.1$), “blood pressure” ($e = 0.2$), “sleep” ($e = 0.3$) and “age” ($e = 0.3$) (**Figure 3A**). This summary, however, is not representative of each unique trait, as the specific obesity trait, belonging to the “anthropometric measurement” category, is highly over-represented ($e = 15$) among other under-represented traits (**Figure 3B**). Next, we summarized cross-traits with their respective associated-SNP beta coefficients to study the direction of effect of each phenotype as compared to leptin (**Figure 3C**). Consistent monodirectional effects with leptin were determined with body mass index (mean effect with leptin (me) = +0.063), body fat percentage ($me = +0.342$), BMI-adjusted hip circumference ($me = +0.024$), bone mineral density ($me = +0.025$), and obesity ($me = +0.277$). Opposite directions, however, were found

with hyperlipidemia (me = 0.253), insulin-like growth factor-binding protein 1 (me = -0.134), insulin sensitivity measurement (me = -0.200), and the other adipokines, adiponectin (me = -0.107) and leptin receptor measurements (me = -0.114). Finally, some traits present mixed effects with leptin levels, such as type-2 diabetes, addiction-related traits (intakes of alcohol and coffee, smoking behavior, substance use), high density lipoprotein cholesterol, and some taste preferences such as sweetened drinks and sugar intake. The distribution of the cross-trait across leptin genetic blocks was heterogeneous (**Table 1**).

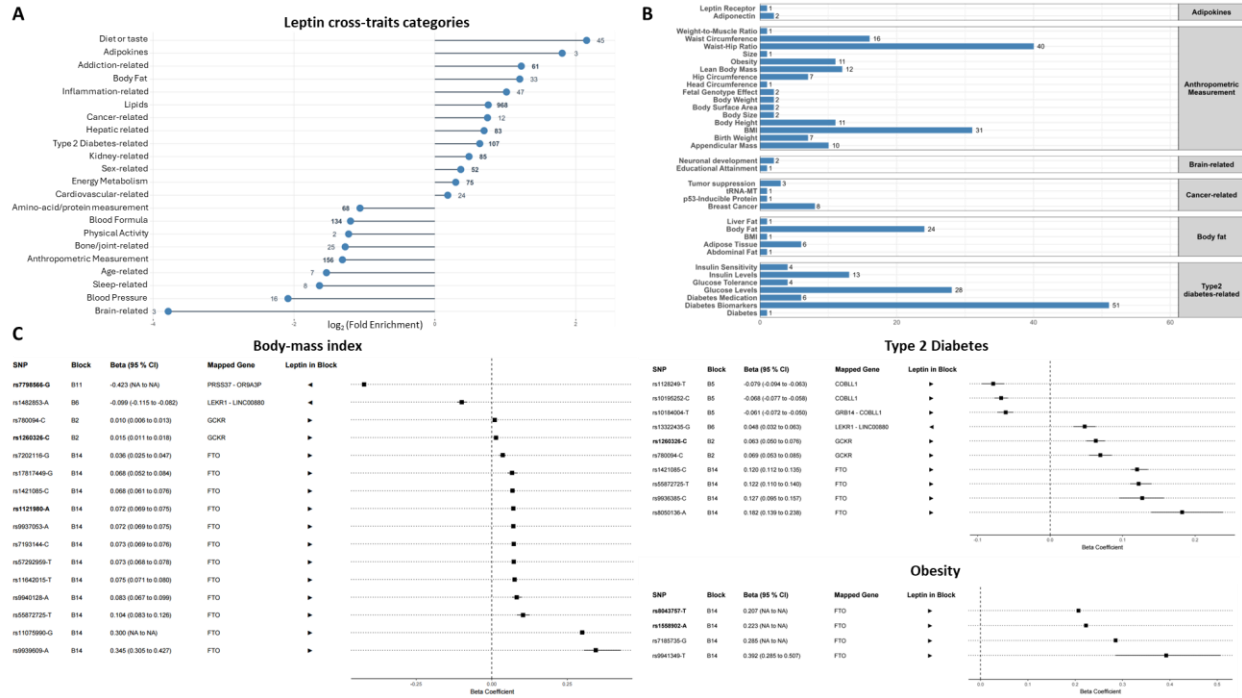


Figure 3. Cross-traits associated with leptin levels. (A) Normalized fold-enrichment values for the 22 categories of traits associated with leptin measurement and BMI-adjusted leptin measurement. (B) Raw counts for “adipokines”, “anthropometric measurement”, “brain-related”, “cancer-related”, “body fat” and “type-2-diabetes-related” cross-trait categories. (C) Forest plots showing the direction of effect of the traits as compared to leptin levels in each genetic block. Beta coefficients represent the increase or decrease per unit in the outcome for each significantly associated trait ($p < 5e-08$).

Gene-based pleiotropic network. Concomitantly to the cross-trait analysis, we conducted a protein network reconstruction around leptin. We first extracted 57 protein-coding genes overlapping the genetic blocks of leptin (**Table 1**, 4 genes were associated with consecutive blocks). These input genes were used in STRING-db to map out the functional protein modules involved in leptin molecular functions (**Figure 1**, see Methods). A preliminary functional annotation of the network was done using the Phenotype-Genotype Integrator (PheGenI) library, to explore the diseases and traits associated with the input genes (**Figure 4A**). The analysis confirmed a highly significant association with the leptin phenotype ($e = 19$), and revealed other enriched associations with phenotypes including type-2 diabetes, body-mass index, obesity, abdominal fat and metabolic syndrome X. This initial network was augmented with 57 first-shell

interactors at a confidence score of 0.5, and clustered using the k-means algorithm. This network expansion identified newly enriched or depleted, as well as gain/loss of PhenGenI terms (**Figure 4B**), with a noticeable decrease in the leptin phenotype ($e = 9.5$), and increases in metabolic syndrome X, type-2 diabetes, and glucose tolerance test (term gain).

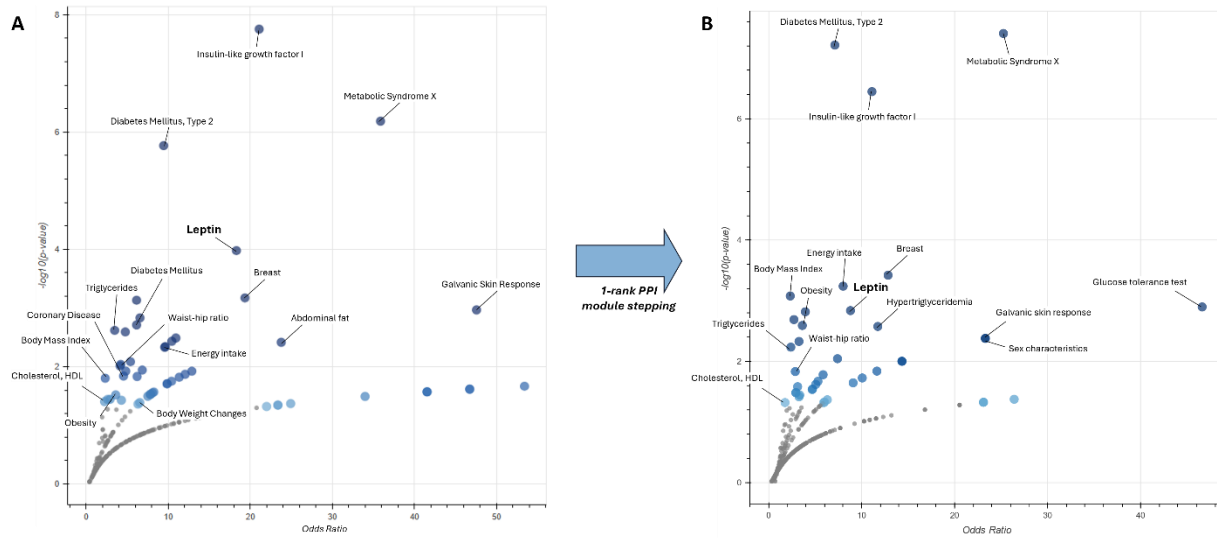


Figure 4. PPI network augmentation allows for biological term exploration. (A) PhenGenI trait/disease enriched terms with the 57 leptin-related proteins. **(B)** PhenGenI trait/disease enriched terms after 1-rank PPI stepping with 57 additional 1st-shell interactors, highlighting enriched and depleted terms after augmentation.

On the other hand, the expanded PPI network was clustered into 9 PPI modules by k-means clustering, and each module was functionally annotated for biological pathways, ontological terms and diseases. Leptin-related proteins not interacting with the network were discarded. Each of the 9 resulting PPI modules governed specific biological functions, the central-one related to leptin and body-mass index, and others linked with either ciliary function and development, triglycerides and cardiovascular diseases, neuronal signaling and related disorders, or endocrine cell differentiation (**Figure 5**).

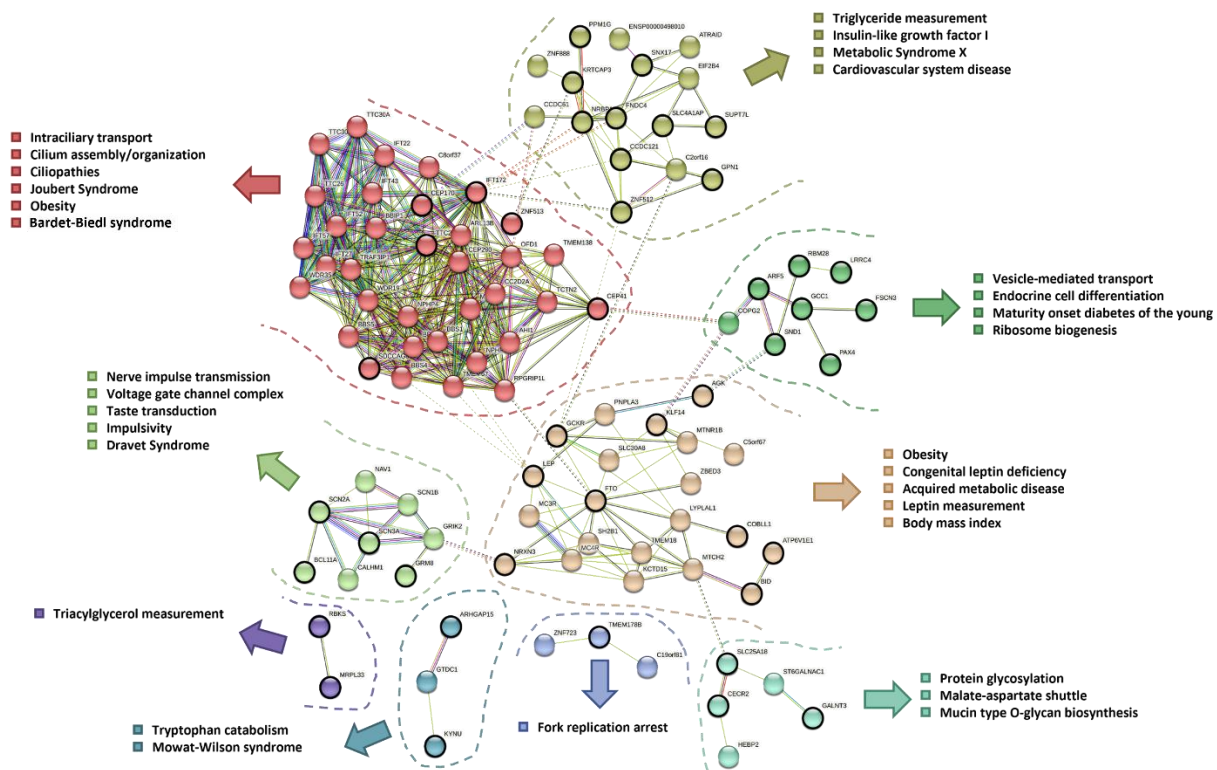


Figure 5. Augmented PPI network around leptin-related proteins. PPI network of the initial query proteins plus the 1st-shell interactors, clustered using the k-means algorithm. Leptin-related proteins are highlighted in black. Detached nodes (non-interacting proteins) were removed. Annotations for the main associated function, pathway, or disease accompany each cluster.

Discussion

Conducting the cross-traits analysis allowed for the identification of the phenotypes sharing unique genetic associations with serum leptin levels. These traits could be organized into 22 distinct categories impacting diverse functions and tissues, underlying leptin high pleiotropic effects in human. Specific categories showed depletion against background (brain-related, blood pressure, sleep and age-related), potentially indicating function specificity for distinct SNPs within general and/or subjective categories regrouping heterogeneous traits, or that leptin is functionally distant or indirectly linked with these traits and is hence less associated with them than random GWAS loci. On the other hand, high enrichment values were observed for diet, adipokines, addiction or obesity -related traits, suggesting shared underlying mechanisms with leptin levels and extended genetic overlap, pointing to potential functional regrouping and biological relevance of these traits in leptin's pleiotropy.

Functional consequences of these traits are highlighted by their effect directions with leptin serum levels, which largely confirmed physiological and mechanical scientific literature in patients and animal models: homodirectional effects between leptin and body mass index (27) and obesity (28), and opposite effects

with hyperlipidemia (29) and the long-guessed reverse balance with other adipokines such as adiponectin, which we confirm at a genetic level with this study.

We also provide a network of biological functions and pathways explaining these pleiotropic phenotypes. Upon expanding the PPI network around the leptin gene, we identified pathways linking leptin signaling and obesity to a cluster of proteins specialized in development and embryogenesis (especially ciliogenesis), a module of proteins governing metabolism regulation, a cluster implicated in endocrine regulation and cellular function, and a module of genes responsible for neuronal signaling and disorders. This echoes previous studies conducted on the implications of leptin in neuronal development, specifically that in the hypothalamus (29) where postnatal leptin acts as a neurotrophic factor and helps axonal growth within the arcuate nucleus, constructing the leptin-melanocortin neuronal pathway, which they will activate later in life to control satiety, energy intake and subsequent lipid metabolism.

A notable feature of network expansion is that it helps prioritize genes linked with the GWAS variants. This augmentation allows i) for a discard of the proteins that cannot interact with the PPI modules, which could stem from a wrong mapping of the corresponding genes in the GWAS studies, and ii) for a recovery, by adding functional interactors, of genes that were not associated by GWAS or mapped in later stages.

The conducted study paves the way for further research aiming to elucidate obesity's physiopathology. A global correlation analysis by LD regression score between leptin and some of the identified cross-traits would hint at the overall genetic association between the traits. Moreover, causality between modifiable risk factors in a disease or phenotype and the individual's health outcomes can be deciphered with Mendelian randomizations (30). By conducting systematic MR between all possible cross-traits identified with leptin, one would be able to reconstruct the causal inference network, with the direction of causality between each linked trait. MR could be achieved using GWAS summary statistics for leptin and a number of traits and is also made possible with access to large cohorts like the UK BioBank, for which genomes and exomes are available for more than 500.000 individuals.

References

1. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009 Mar 25;9:88.
2. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity*. 2022 Jan 11;55(1):31–55.
3. Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M, Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol*. 2004 Aug;33(4):751–8.

4. Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. *Int J Cancer*. 2001 Feb 1;91(3):421–30.
5. Pati S, Irfan W, Jameel A, Ahmed S, Shahid RK. Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers (Basel)*. 2023 Jan 12;15(2):485.
6. Harvie M, Hooper L, Howell A h. Central obesity and breast cancer risk: a systematic review. *Obesity Reviews*. 2003;4(3):157–73.
7. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003 Aug 20;95(16):1218–26.
8. Paracchini V, Pedotti P, Taioli E. Genetics of Leptin and Obesity: A HuGE Review. *American Journal of Epidemiology*. 2005 Jul 15;162(2):101–14.
9. De Matteis R, Puxeddu R, Riva A, Cinti S. Intralobular ducts of human major salivary glands contain leptin and its receptor. *J Anat*. 2002 Nov;201(5):363–70.
10. Bjørbaek C, Kahn BB. Leptin signaling in the central nervous system and the periphery. *Recent Prog Horm Res*. 2004;59:305–31.
11. Park HK, Ahima RS. Leptin signaling. *F1000Prime Rep*. 2014;6:73.
12. Tam V, Patel N, Turcotte M, Bossé Y, Paré G, Meyre D. Benefits and limitations of genome-wide association studies. *Nat Rev Genet*. 2019 Aug;20(8):467–84.
13. Comuzzie AG, Cole SA, Laston SL, Voruganti VS, Haack K, Gibbs RA, et al. Novel genetic loci identified for the pathophysiology of childhood obesity in the Hispanic population. *PLoS One*. 2012;7(12):e51954.
14. Meeks KAC, Bentley AR, Gouveia MH, Chen G, Zhou J, Lei L, et al. Genome-wide analyses of multiple obesity-related cytokines and hormones informs biology of cardiometabolic traits. *Genome Med*. 2021 Oct 7;13(1):156.
15. Wang X, Jia J, Huang T. Shared genetic architecture and casual relationship between leptin levels and type 2 diabetes: large-scale cross-trait meta-analysis and Mendelian randomization analysis. *BMJ Open Diabetes Res Care*. 2020 Apr;8(1):e001140.
16. Ortega-Azorín C, Coltell O, Asensio EM, Sorlí JV, González JI, Portolés O, et al. Candidate Gene and Genome-Wide Association Studies for Circulating Leptin Levels Reveal Population and Sex-Specific Associations in High Cardiovascular Risk Mediterranean Subjects. *Nutrients*. 2019 Nov 13;11(11):2751.
17. MacArthur J, Bowler E, Cerezo M, Gil L, Hall P, Hastings E, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res*. 2017 Jan 4;45(D1):D896–901.
18. R: The R Project for Statistical Computing [Internet]. 2025 [cited 2025 Mar 14]. Available from: <https://www.r-project.org/>
19. Gel B, Serra E. karyoploteR: an R/Bioconductor package to plot customizable genomes displaying arbitrary data. *Bioinformatics*. 2017 Oct 1;33(19):3088–90.
20. Myers TA, Chanock SJ, Machiela MJ. LDlinkR: An R Package for Rapidly Calculating Linkage Disequilibrium Statistics in Diverse Populations. *Front Genet* [Internet]. 2020 Feb 28 [cited 2025 Mar 14];11. Available from: <https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2020.00157/full>
21. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*. 2015 Nov 1;31(21):3555–7.
22. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res*. 2019 Jan 8;47(D1):D607–13.

23. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res.* 2023 Jan 6;51(D1):D638–46.
24. Chen EY, Tan CM, Kou Y, Duan Q, Wang Z, Meirelles GV, et al. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. *BMC Bioinformatics.* 2013 Apr 15;14:128.
25. Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z, et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. *Nucleic Acids Res.* 2016 Jul 8;44(Web Server issue):W90–7.
26. Xie Z, Bailey A, Kuleshov MV, Clarke DJB, Evangelista JE, Jenkins SL, et al. Gene Set Knowledge Discovery with Enrichr. *Current Protocols.* 2021;1(3):e90.
27. Kennedy A, Gettys TW, Watson P, Wallace P, Ganaway E, Pan Q, et al. The Metabolic Significance of Leptin in Humans: Gender-Based Differences in Relationship to Adiposity, Insulin Sensitivity, and Energy Expenditure*. *The Journal of Clinical Endocrinology & Metabolism.* 1997 Apr 1;82(4):1293–300.
28. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, et al. Leptin and Obesity: Role and Clinical Implication. *Front Endocrinol (Lausanne).* 2021;12:585887.
29. Bouret SG. Neurodevelopmental actions of leptin. *Brain Res.* 2010 Sep 2;1350:2–9.
30. Guo Z, Du H, Guo Y, Jin Q, Liu R, Yun Z, et al. Association between leptin and NAFLD: a two-sample Mendelian randomization study. *Eur J Med Res.* 2023 Jul 3;28:215.