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COMPREHENSIVE BIOINFORMATICS ANALYSIS OF OBESITY

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Abstract:

Obesity is a multifactorial metabolic disorder associated with excessive fat accumulation and increased risk of diseases such as type 2 diabetes, cardiovascular disorders, and hypertension. This study aimed to identify key genes and molecular pathways involved in obesity using an integrative bioinformatics approach. A total of 30 obesity-associated genes were retrieved from the DisGeNET database and analyzed using STRING for protein–protein interactions, GeneMANIA for gene interaction networks, and Enrichr and Reactome for functional and pathway enrichment analysis. The interaction network revealed strong connectivity among the genes, with major hub genes including INS, LEP, TNF, IL6, and POMC, indicating their central role in metabolic regulation and inflammation. Gene Ontology analysis showed significant enrichment in biological processes such as regulation of lipid localization (signal = 3.23), hormone secretion (signal = 3.20), and feeding behavior (signal = 3.19). Additional enrichment in glucose homeostasis and insulin signaling further highlighted metabolic involvement. GeneMANIA and Enrichr analyses confirmed strong functional associations related to appetite regulation, adipogenesis, and hormonal imbalance. Reactome pathway analysis identified key pathways including peptide hormone metabolism and ghrelin signaling. Overall, the study demonstrates that obesity is regulated by interconnected metabolic, hormonal, and behavioral pathways, providing insights for multi-target therapeutic strategies.

Keywords: *Network Biology, Hub Genes, Bioinformatics, Systems Biology.*

Introduction

Obesity is a multifactorial metabolic disorder characterized by excessive fat accumulation, which is a significant risk to global health. Obesity is closely linked with various metabolic disorders, including type 2 diabetes mellitus, cardiovascular disease, hypertension, and various cancers. Obesity is increasing rapidly, especially due to a sedentary lifestyle, high-calorie diet, genetic factors, and hormonal imbalance, which is a serious health concern worldwide (1). At the molecular level, obesity is regulated by a complex network of genes that regulate appetite,

lipid metabolism, insulin, energy expenditure, and inflammation. Various key hormones, such as leptin, insulin, ghrelin, and glucagon-like peptides, have a critical role to play in maintaining energy homeostasis by modulating various central and peripheral signals (2). Abnormal regulation of these signals leads to changes in appetite, abnormal lipid metabolism, abnormal glucose metabolism, and low-grade inflammation, which is characteristic of obesity.

The current available anti-obesity medications focus mainly on the suppression of appetite, fat absorption, and glucose metabolism. Orlistat, Liraglutide, and Semaglutide have proven to be effective in reducing weight in obese patients. Nevertheless, their long-term use is restricted due to side effects such as gastrointestinal discomfort, nausea, cardiovascular complications, and low patient compliance (3). Additionally, most of these medications target single genes or proteins, whereas obesity is a complex disorder regulated by multiple genes or proteins. This emphasizes the need for the identification of novel molecular targets for effective obesity therapy.

The discovery of novel anti-obesity medications is a complex process that requires an in-depth understanding of gene–gene interactions, gene regulatory networks, and biological pathways in the context of disease progression. Bioinformatics is an important drug discovery technology that facilitates the analysis of large datasets for identifying gene-disease relationships, protein-protein interactions, and functional pathway enrichment. Bioinformatics is useful in identifying key genes or genes in a pathway that may be targeted for drug therapy (4).

For this study, a bioinformatics-based approach has been followed to investigate obesity-related genes by utilizing various bioinformatics tools and databases. Gene-disease association data have been obtained and further explored by investigating protein-protein interaction networks using STRING bioinformatics tool. Functional enrichment analysis has also been carried out to identify significant biological processes involved in lipid metabolism, hormone secretion, feeding behavior, insulin signaling, and adipose tissue development. Pathway analysis has also been done by utilizing Reactome and other enrichment visualization tools to understand the role of obesity-related genes in various pathways involved in obesity.

For this study, bioinformatics tools have been used to identify obesity-associated genes and explore various protein-protein interactions and enriched biological processes involved in obesity-related metabolic disorders.

Methodology

1. Retrieval of obesity-associated genes (DisGeNET)

Genes associated with obesity were identified using the DisGeNET database by querying the disease term “obesity”. DisGeNET integrates information from curated repositories, genome-wide association studies and scientific literature, thereby providing experimentally supported gene–disease associations. All genes showing significant association with obesity were collected and duplicates were removed to generate the primary gene dataset. This dataset served as the foundation for subsequent interaction and functional enrichment analyses (5).

2. Protein–protein interaction network analysis (STRING)

Protein–protein interaction (PPI) analysis was conducted using the STRING database to study interactions among obesity-associated genes. STRING predicts functional associations based on experimental data, co-expression, database annotations and literature mining. The interaction network revealed highly connected genes and enriched biological processes including lipid regulation, hormone secretion and feeding behavior (6).

3. Gene interaction and functional association analysis (GeneMANIA)

The collected genes were analyzed using GeneMANIA to explore gene–gene interactions and functional similarity. GeneMANIA predicts gene function by integrating datasets including co-expression, co-localization, shared protein domains, pathways and genetic interactions. The generated network also predicted additional related genes associated with metabolic regulation and energy balance (7).

4. Regulatory enrichment analysis (Enrichr)

The complete gene set was subjected to enrichment analysis using the Enrichr web server to identify transcriptional regulators, epigenetic signatures and microRNA targets. Enrichr performs gene set enrichment using multiple biological libraries and statistical ranking methods to identify regulatory mechanisms controlling gene expression (8).`

5. Pathway enrichment analysis (Reactome)

Pathway enrichment analysis was performed using the Reactome database to identify biological pathways significantly associated with the gene set. Reactome is a curated pathway knowledgebase that maps genes to molecular reactions and biological processes involved in metabolism and signaling (9).

Results

1. Disgenet

A total of 30 genes associated with obesity were selected based on curated disease–gene association evidence from public databases, including MC4R, ADRB3, LEP, LEPR, POMC, FTO, TNF, ADCY3, INS, PPARG, GHRL, IL6, CARTPT, ADIPOQ, APOE, SIRT1, UCP3, CCL2, NAMPT, CRP, PCSK1, SH2B1, RETN, GIP, SIM1, GLP1R, AGRP, BDNF, DRD2, and GIPR

2. STRING analysis

STRING was used to construct a protein–protein interaction network for Obesity-associated genes.

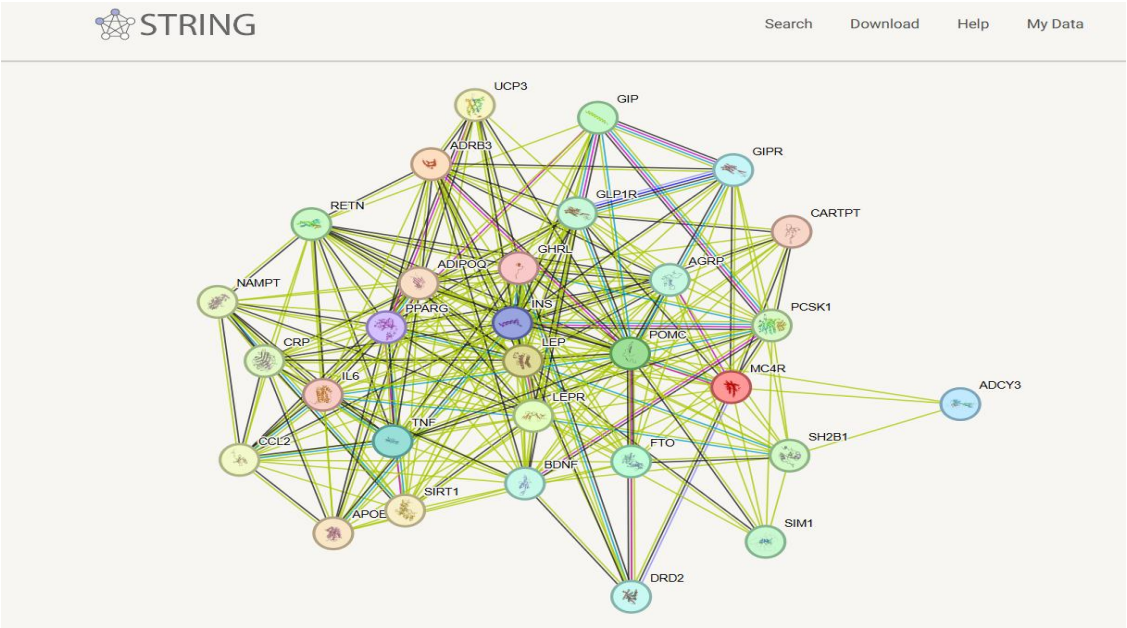

Figure 1: Protein-protein interaction network of 30 obesity-associated genes using STRING

Table 1: Gene list from the tool DisGeNET

Gene	Gene Full Name	N diseases	N variants	Score
MC4R	melanocortin 4 receptor	19	116	1
ADRB3	adrenoceptor beta 3	24	3	1
LEP	leptin	63	70	1
LEPR	leptin receptor	72	115	1
POMC	proopiomelanocortin	116	44	1
FTO	FTO alpha-ketoglutarate dependent protein	37	261	1
TNF	tumor necrosis factor	312	9	1
ADCY3	adenylate cyclase 3	8	40	1
INS	insulin	96	65	1
PPARG	peroxisome proliferator activated receptor gamma	79	121	1
GHRL	ghrelin and obestatin prepropeptide	27	4	1
IL6	interleukin 6	214	9	1
CARTPT	CART prepropeptide	13	1	1
ADIPOQ	adiponectin, C1Q and collagen domain containing	44	6	1
APOE	apolipoprotein E	105	46	1
SIRT1	sirtuin 1	62	3	1
UCP3	uncoupling protein 3	11	11	1
CCL2	C-C motif chemokine ligand 2	102	2	1
NAMPT	nicotinamide phosphoribosyltransferase	8	1	1
CRP	C-reactive protein	67	1	1
PCSK1	proprotein convertase subtilisin/kexin type 1	5	113	1
SH2B1	SH2B adaptor protein 1	6	48	1
RETN	resistin	13	1	1
GIP	gastric inhibitory polypeptide	3	15	1
SIM1	SIM bHLH transcription factor 1	10	63	1
GLP1R	glucagon like peptide 1 receptor	9	17	1
AGRP	agouti related neuropeptide	4	2	1
BDNF	brain derived neurotrophic factor	63	37	1
DRD2	dopamine receptor D2	61	57	1
GIPR	gastric inhibitory polypeptide receptor	6	15	1

The network consisted of 30 interacting genes, indicating strong functional connectivity related to psoriasis.The generated interaction network demonstrated strong connectivity among the proteins, suggesting coordinated molecular activity. Several genes showed multiple interactions, indicating their potential role as key regulatory or hub genes involved in obesity.

Gene ontology analysis was performed to identify enriched biological processes associated with the gene set.

Table 2: Gene ontology biological processes lists

GO Term	Description	Count (Network)	Strength	Signal	FDR
GO:0046883	Regulation of hormone secretion	13 of 239	1.55	3.20	1.37E-13
GO:1905952	Regulation of lipid localization	11 of 167	1.64	3.23	2.00E-12
GO:0050795	Regulation of behaviour	8 of 72	1.86	3.22	1.98E-10
GO:0060259	Regulation of feeding behaviour	6 of 26	2.18	3.19	2.87E-09
GO:0048521	Negative regulation of behaviour	5 of 12	2.44	3.13	1.02E-08
GO:0010883	Regulation of lipid storage	7 of 50	1.96	3.12	1.20E-09
GO:0043434	Response to peptide hormone	13 of 355	1.38	2.54	3.15E-12
GO:0031667	Response to nutrient levels	15 of 461	1.33	2.50	2.56E-13
GO:0007631	Feeding behaviour	7 of 88	1.72	2.49	2.18E-08
GO:0046887	Positive regulation of hormone secretion	8 of 127	1.62	2.48	6.57E-09
GO:0010817	Regulation of hormone levels	16 of 525	1.30	2.45	1.31E-13
GO:0003008	Regulation of blood pressure	9 of 191	1.49	2.31	4.10E-09
GO:0042593	Glucose homeostasis	9 of 196	1.48	2.28	4.89E-09
GO:0050796	Regulation of insulin secretion	8 of 153	1.54	2.25	2.10E-08
GO:0032868	Response to insulin	9 of 205	1.46	2.22	6.60E-09

The Gene Ontology enrichment analysis for the selected gene set indicated that the genes were significantly enriched in biological processes such as hormonal regulation, metabolism, and behavior. Among the top enriched biological processes in the selected genes, the regulation of lipid localization (GO:1905952) had the highest signal value of 3.23. This is followed by the regulation of behavior (GO:0050795), which also had a high signal value of 3.22. The regulation of hormone secretion (GO:0046883) also showed a high signal value of 3.20. It is also interesting to note that the regulation of feeding behavior (GO:0060259) and the negative regulation of behavior (GO:0048521) also showed high signal values of 3.19 and 3.13, respectively, with high strengths of 2.18 and 2.44. Metabolic pathways were also well represented, as indicated by the positive regulation of lipid storage, which had a signal of 3.12, strength of 1.96, and FDR of 1.20×10^{-9}, as well as the regulation of glucose homeostasis, with a signal of 2.28, strength of 1.48, and FDR of 4.89×10^{-9}. The role of hormonal and endocrine pathways was also indicated, as suggested by the positive regulation of hormone secretion, with a signal of 2.48, strength of 1.62, and FDR of 6.57×10^{-9}, the regulation of hormone levels, with a signal of 2.45, strength of 1.30, and FDR of 1.31×10^{-13}, as well as the regulation of insulin secretion, with a signal of 2.25, strength of 1.54, and FDR of 2.10×10^{-8}. Other

pathways, such as the response to nutrient levels, with a signal of 2.50, strength of 1.33, and FDR of 2.56×10^{-13}, as well as the response to peptide hormone, with a signal of 2.54, strength of 1.38, and FDR of 3.15×10^{-12}, further emphasize the metabolic sensitivity of the gene set.

3. GeneMania network analysis

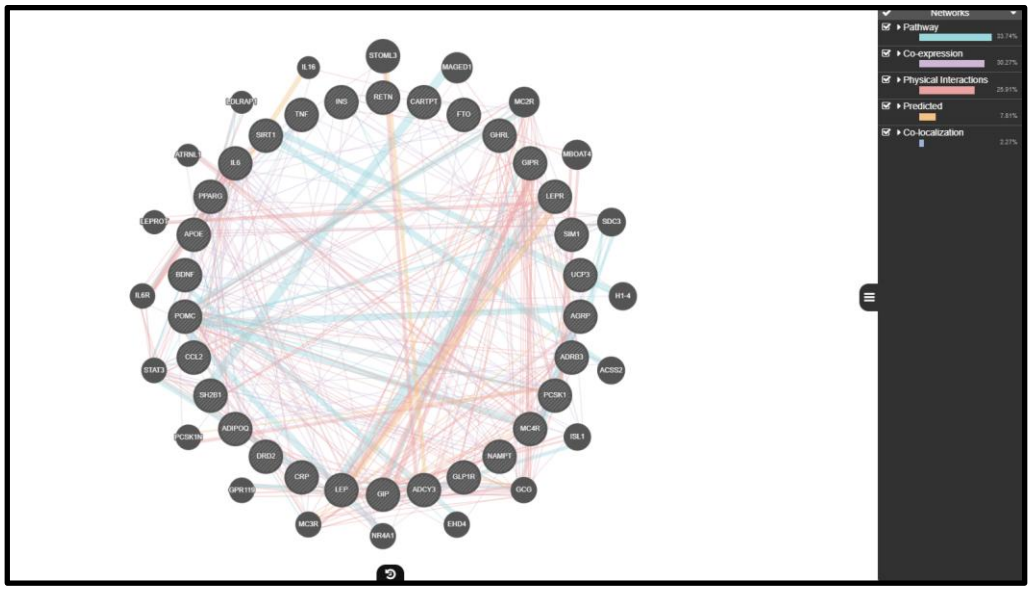

Figure 2: GeneMANIA network displaying different interaction types such as co-expression,physical interactions, and predicted associations

The GeneMANIA network analysis identified a highly interconnected network of gene interactions. Several of the genes appeared to function as central nodes or hubs within the network, based on their connectivity. The most prominent of these hub genes were the INS, LEP, TNF, IL6, and POMC genes. These were found to be central nodes within the network and had a high degree of connectivity with other nodes. This suggests their potential role in the regulation of the associated biological processes. Several other genes, including the LEPR, MC4R, PPARG, and ADIPOQ genes, were also found to have a significant degree of connectivity. These were found to function as secondary nodes within the network. The interaction network of the genes included different types of interactions. The most prominent of these were the co-expression, physical interactions, and the predicted interactions. This suggests a functional consensus within the network of the involved genes. The network of interactions between the genes indicates a highly integrated system of regulation involving the different biological processes. The hub genes within the network appear to play a critical role in the regulation of the associated biological processes.

4. Enrichr functional enrichment

The Enrichr analysis provided an overview of functional enrichment across multiple gene set libraries. The results indicated that the obesity-associated genes were significantly enriched in gene sets related to appetite regulation, adipogenesis, insulin signaling, leptin-mediated pathways, and adipose tissue inflammation. This enrichment profile confirms the functional relevance of the selected genes and supports their role in mechanisms underlying excessive fat accumulation and body weight regulation. The identified enrichment patterns further suggest coordinated involvement of energy intake control, fat storage processes, hormonal imbalance, and obesity-associated metabolic inflammation contributing to disease development.

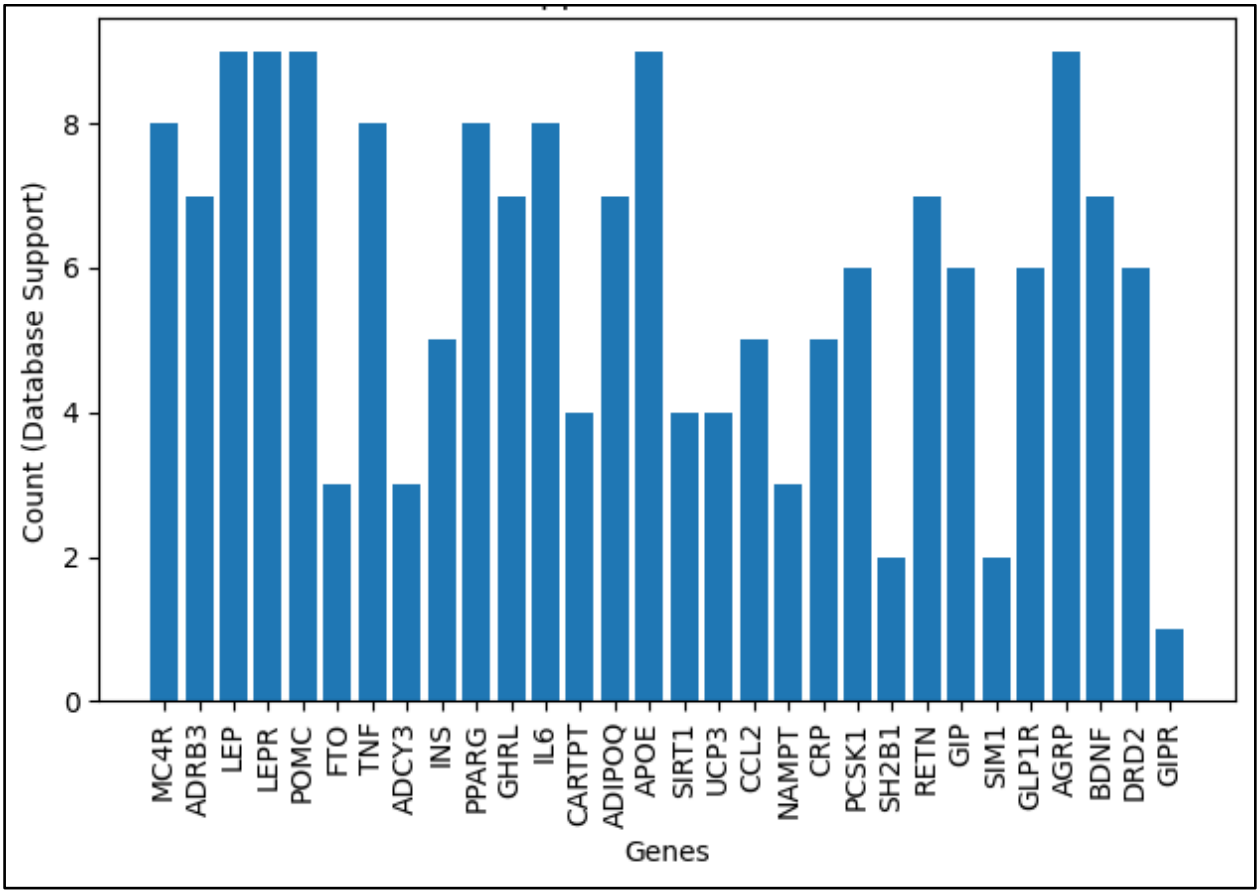

Figure 3: Gene Support Across Databases

Genes with higher counts are more consistently reported and are likely more important in the biological process being studied. A few genes stand out clearly. LEP, LEPR, POMC, APOE, and AGRP are supported by the highest number of databases (9), which means there is strong agreement across different sources about their role. These can be considered the most reliable and important genes in this analysis. Some other genes like MC4R, TNF, PPARG, and IL6 also show strong support (count of 8), indicating they play major roles, especially in metabolism and inflammation. Many genes fall in the middle range (5–7), showing moderate support. These genes are still relevant but may have more specific or secondary roles. A few genes such as FTO, ADCY3, NAMPT, SH2B1, SIM1, and GIPR have low support (less than 4). This means fewer databases report them, so their role may be more limited or less studied.

5. Reactome pathway analysis

The pathway enrichment analysis highlighted metabolism-related and endocrine regulatory pathways involved in obesity pathogenesis. The analysis emphasized pathways associated with adipogenesis, peptide hormone metabolism, ghrelin synthesis and secretion, and FOXO-mediated transcription, indicating their contribution to metabolic imbalance and energy regulation.The identified pathways reflect key physiological processes including appetite control, hormonal signaling, oxidative stress response, and regulation of neuronal-metabolic communication. These pathways are known to play a crucial role in maintaining body weight homeostasis and

adipose tissue function. The enrichment of such pathways further supports the involvement of metabolic dysregulation and endocrine imbalance in the development and progression of obesity.

Figure 4: Reactome pathways highlighting the involvement of selected obesity-associated genes.

Discussion

The current study gives a comprehensive systems-level understanding of obesity by combining gene-disease association, protein-protein interaction, gene regulatory networks, and pathway enrichment analysis. The discovery of 30 obesity-related genes and subsequent analysis have shown a highly interconnected molecular network that supports the multifactorial basis of obesity, which involves both metabolic and hormonal pathways and behaviors. These results are in agreement with previous studies that have shown that obesity is a complex disorder controlled by neuroendocrine and metabolic pathways and not by a single gene effect (1,2).

The protein interaction analysis showed that some genes act as central or "hub" genes, meaning they interact with many other genes and play a major role. Important hub genes identified in this study include INS, LEP, TNF, IL6, and POMC. These genes are already well known in obesity research. For example, insulin controls blood sugar levels, while leptin helps regulate hunger and satiety. Similarly, POMC and MC4R are involved in controlling appetite through the brain. This confirms previous studies that show these genes are critical for maintaining energy balance in the body (2, 10).

The Gene Ontology results further supported this by showing that the genes are mainly involved in processes like hormone secretion, lipid metabolism, feeding behavior, and glucose regulation. The high values observed for lipid localization, behavior regulation, and hormone secretion indicate that obesity is influenced by both metabolic and behavioral factors. This matches earlier findings where obesity is linked to both how the body processes energy and how the brain controls hunger and eating habits (2).

Another important finding was the presence of inflammatory genes such as TNF, IL6, and CRP. These genes are known to be involved in chronic inflammation, which is commonly seen in obese individuals. Previous studies have shown that excess fat tissue releases inflammatory molecules, which can lead to insulin resistance and other metabolic problems (11). Our results support this idea by showing that inflammation is closely linked with metabolic pathways in obesity.

The GeneMANIA analysis also showed that these genes are strongly connected through co-expression and physical interactions. Some genes like LEPR, MC4R, PPARG, and ADIPOQ acted as secondary hubs, linking different biological processes. For example, PPARG plays a role in fat cell formation, and ADIPOQ helps improve insulin sensitivity. This is consistent with studies highlighting the role of adipokines and nuclear receptors in metabolic regulation (12).

The enrichment analysis further highlighted pathways related to appetite control, fat storage, insulin signaling, and hormonal balance. Genes like LEP, LEPR, POMC, APOE, and AGRP were supported by many databases, showing strong agreement about their importance. These genes have also been repeatedly identified in genome-wide association studies as major contributors to obesity risk (13).

Pathway analysis using Reactome showed that processes like ghrelin signaling, peptide hormone metabolism, and adipogenesis are important in obesity. These pathways are directly related to hunger, fat accumulation, and energy balance. This again confirms that obesity is caused by a combination of hormonal imbalance and metabolic dysfunction (2).

Interestingly, some genes like FTO and ADCY3 showed lower support across databases, even though they are known from research studies. This may be because their roles are still being explored or may vary across populations. For example, FTO has been strongly linked with obesity through genetic studies, but its exact mechanism is still under investigation (14).

Conclusion

This study also emphasizes that obesity is a complicated disorder that is controlled by a network of genes rather than a linear pathway. Through the integration of bioinformatics tools, it has also been shown that there are strong interactions between genes related to obesity, with important hub genes such as INS, LEP, TNF, IL6, and POMC being important regulators of metabolism, inflammation, and regulation of food intake. Through functional enrichment, it has also been shown that lipid metabolism, hormone secretion, feeding behavior, and regulation of blood glucose levels are important in obesity.

The presence of inflammatory pathways also reiterates the association of obesity with chronic metabolic disorders. Pathway analysis also reconfirmed the significance of hormonal pathways and energy balance in the progression of the disease. Overall, the results of the study reiterate previous research findings and indicate that for the effective management of obesity, it is crucial to target multiple pathways. These pathways may help in the identification of new targets for the treatment of obesity.

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