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Genetic Polymorphisms in Obesity: How Variants in Lipid Metabolism Genes Contribute to Hyperlipidemia

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ABSTRACT

Obesity is a complex metabolic disorder influenced by both environmental and genetic factors. Among the genetic contributors, polymorphisms in lipid metabolism genes play a significant role in regulating lipid profiles and promoting hyperlipidemia. This review aims to explore the impact of genetic variants on lipid metabolism in individuals with obesity, focusing on genes such as APOE, LPL, FTO, PCSK9, CETP, and FABP. These polymorphisms alter lipid processing, transportation, and storage, leading to aberrant lipid levels, which contribute to hyperlipidemia and subsequent cardiometabolic complications. We will also discuss the gene-environment interactions that modulate these genetic effects and review potential therapeutic interventions targeting lipid metabolism to manage hyperlipidemia in obese individuals.

Keywords: Genetic polymorphisms, obesity, lipid metabolism, hyperlipidemia, gene-environment interactions, cardiometabolic disease

INTRODUCTION

Obesity has emerged as a global epidemic, contributing significantly to the burden of cardiometabolic diseases, including hyperlipidemia, a major risk factor for cardiovascular disease (CVD)[1–3]. Hyperlipidemia is characterized by elevated levels of lipids, including cholesterol and triglycerides, in the bloodstream, which are influenced by genetic predisposition, dietary factors, physical inactivity, and metabolic alterations[4, 5]. Among these factors, genetic polymorphisms in lipid metabolism genes have garnered substantial attention as critical drivers of lipid homeostasis[6–9]. The knowledge of the genetic architecture of obesity and its association with hyperlipidemia is essential for developing precision therapies to manage lipid disorders. This review explores the role of specific genetic polymorphisms that influence lipid metabolism, contribute to the development of hyperlipidemia, and predispose individuals to obesity-related complications.

Genetic Polymorphisms in Lipid Metabolism Genes

Apolipoprotein E (APOE)

The APOE gene encodes apolipoprotein E, a key player in lipid metabolism, particularly in the clearance of triglyceride-rich lipoproteins. The three main APOE isoforms (E2, E3, E4) arise from polymorphisms in the gene, with APOE ε4 being associated with increased low-density lipoprotein (LDL) cholesterol and higher cardiovascular risk in obese individuals. Conversely, APOE ε2 is associated with reduced LDL levels but an increased risk of hypertriglyceridemia[10–13]. The impact of APOE polymorphisms on lipid levels may be more pronounced in individuals with obesity, as the adiposity-related metabolic dysfunction exacerbates the influence of these variants on lipid transport and clearance[14, 15]. Individuals carrying the APOE ε4 allele are more likely to develop hyperlipidemia when exposed to high-fat diets, highlighting the gene-environment interaction in obesity[16, 17].

Lipoprotein Lipase (LPL)

Lipoprotein lipase (LPL) is an enzyme crucial for the hydrolysis of triglycerides in lipoproteins, releasing free fatty acids for storage or energy use. Genetic polymorphisms in the LPL gene, such as rs328 and rs268, are linked to alterations in triglyceride levels, particularly in obese individuals. Carriers of LPL polymorphisms have an impaired capacity to clear triglyceride-rich lipoproteins, leading to hypertriglyceridemia, which is commonly observed in obesity-induced hyperlipidemia[18, 19].

Furthermore, polymorphisms in LPL can modify the response to dietary fat intake, with certain variants exacerbating lipid abnormalities when combined with a high-fat diet, underscoring the

interplay between genetics and lifestyle in lipid dysregulation.[20, 21]

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

The PCSK9 gene regulates LDL receptor degradation, controlling plasma LDL cholesterol levels. Gain-of-function mutations in PCSK9 lead to hypercholesterolemia by reducing the number of LDL receptors available to clear circulating LDL cholesterol. Conversely, loss-of-function mutations result in lower LDL cholesterol levels and reduced cardiovascular risk[22, 23].

In obese individuals, PCSK9 polymorphisms exacerbate the lipid imbalance, leading to hypercholesterolemia and increasing the risk of atherosclerosis. Targeting PCSK9 with monoclonal antibodies has become an effective therapeutic strategy to manage hyperlipidemia, particularly in individuals with genetic predispositions linked to PCSK9 variants[24].

Fat Mass and Obesity-Associated Gene (FTO)

The FTO gene has been extensively studied for its association with obesity and lipid metabolism. Polymorphisms in FTO influence body mass index (BMI), fat distribution, and lipid profiles[25]. The rs9939609 variant is the most well-characterized, with carriers showing an increased risk of obesity and higher triglyceride and LDL cholesterol levels. Although the exact mechanisms remain unclear, it is hypothesized that FTO variants contribute to altered energy homeostasis and lipid storage, leading to an increased prevalence of hyperlipidemia in obese individuals. Additionally, environmental factors such as diet can modify the effect of FTO polymorphisms on lipid metabolism, amplifying the risk of hyperlipidemia in those with an unhealthy diet.[25]

Cholesteryl Ester Transfer Protein (CETP)

The CETP gene encodes a protein involved in the transfer of cholesteryl esters and triglycerides between lipoproteins. Polymorphisms such as rs5882 in the CETP gene are associated with variations in high-density lipoprotein (HDL) cholesterol levels. Individuals carrying the rs5882 variant tend to have lower HDL cholesterol and higher triglyceride levels, contributing to the lipid abnormalities observed in obese individuals.[26] The dysregulation of CETP function in individuals with obesity further complicates the lipid profile, increasing the risk of hyperlipidemia and CVD. Therapeutic agents that inhibit CETP activity have shown promise in raising HDL cholesterol levels and improving lipid profiles in those with hyperlipidemia driven by genetic polymorphisms[26].

Fatty Acid Binding Protein (FABP)

The FABP family of genes encodes intracellular lipid chaperones that facilitate the uptake and trafficking of fatty acids. Polymorphisms in FABP genes, such as FABP2 rs1799883, are associated with increased intestinal absorption of dietary fats and elevated circulating triglyceride levels[27]. Obese individuals with FABP2 polymorphisms are more prone to developing hyperlipidemia due to the enhanced lipid absorption and storage. The interaction between FABP gene variants and diet plays a pivotal role in determining lipid metabolism outcomes, suggesting that dietary interventions may mitigate the adverse effects of these polymorphisms on lipid profiles in obese individuals[27].

Gene-Environment Interactions and Hyperlipidemia

The interplay between genetic predispositions and environmental factors, such as diet and physical activity, significantly influences lipid metabolism in obese individuals. While genetic polymorphisms predispose individuals to dysregulated lipid profiles, lifestyle factors often act as catalysts, exacerbating the metabolic imbalance[28]. For instance, a high-fat diet can amplify the adverse effects of APOE, LPL, and FTO polymorphisms, leading to more pronounced hyperlipidemia. Understanding these gene-environment interactions provides valuable insights into personalized therapeutic strategies, including dietary modifications and pharmacological interventions tailored to an individual's genetic makeup.

Therapeutic Approaches Targeting Genetic Polymorphisms

Given the role of genetic polymorphisms in lipid metabolism and hyperlipidemia, therapeutic interventions targeting these genetic variants have gained traction. PCSK9 inhibitors have emerged as a potent treatment for hypercholesterolemia in individuals with PCSK9 mutations, effectively lowering LDL cholesterol levels. Similarly, CETP inhibitors aim to improve HDL cholesterol levels in individuals with CETP polymorphisms. Nutritional interventions, such as omega-3 fatty acid supplementation, may also help mitigate hyperlipidemia in individuals with FABP and APOE polymorphisms by reducing triglyceride levels. Genetic screening and personalized medicine approaches can further optimize treatment strategies for managing hyperlipidemia in obese individuals with genetic predispositions.

CONCLUSION

Genetic polymorphisms in lipid metabolism genes play a critical role in the development of hyperlipidemia in obese individuals. Variants in APOE, LPL, PCSK9, FTO, CETP, and FABP alter lipid processing, contributing to dyslipidemia and increasing the risk of cardiovascular disease. Understanding the gene-environment interactions that modulate lipid metabolism provides opportunities for personalized therapeutic interventions to manage hyperlipidemia in obesity. Future research should focus on exploring novel genetic variants and developing targeted therapies to reduce the burden of obesity-related lipid disorders.

REFERENCES

1. Balderas-Peña, L.-M.-A., Sat-Muñoz, D., Mireles-Ramírez, M.-A., Martínez-Herrera, B.-E., Nava-Zavala, A.-H., Cervantes-González, L.-M., Muñoz-García, M.-G., Rubio-Jurado, B., Páramo, M.S., Sánchez, E.G., Nuño-Guzmán, C.-M., Balderas-Peña, L.-M.-A., Sat-Muñoz, D., Mireles-Ramírez, M.-A., Martínez-Herrera, B.-E., Nava-Zavala, A.-H., Cervantes-González, L.-M., Muñoz-García, M.-G., Rubio-Jurado, B., Páramo, M.S., Sánchez, E.G., Nuño-Guzmán, C.-M.: Influence of Chronic Low-Grade Inflammation (Obesity) on the Systemic Inflammatory Response. In: Multisystem Inflammatory Syndrome - Natural History. IntechOpen (2023)
2. Calcaterra, V., Verduci, E., Milanta, C., Agostinelli, M., Bona, F., Croce, S., Valsecchi, C., Avanzini, M.A., Zuccotti, G.: The Benefits of the Mediterranean Diet on Inflamm-Aging in Childhood Obesity. Nutrients. 16, 1286 (2024). https://doi.org/10.3390/nu16091286
3. Cheng, L., Wang, J., Dai, H., Duan, Y., An, Y., Shi, L., Lv, Y., Li, H., Wang, C., Ma, Q., Li, Y., Li, P., Du, H., Zhao, B.: Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. Adipocyte. 10, 48–65. https://doi.org/10.1080/21623945.2020.1870060
4. Uti, D.E., Ibiam, U.A., Omang, W.A., Udeozor, P.A., Umoru, G.U., Nwadum, S.K., Bawa, I., Alum, E.U., Mordi, J.C., Okoro, E.O., Obeten, U.N., Onwe, E.N., Zakari, S., Opotu, O.R., Aja, P.M.: Buchholzia coriacea Leaves Attenuated Dyslipidemia and Oxidative Stress in Hyperlipidemic Rats and Its Potential Targets in Silico. Pharmaceutical Fronts. 05, e141–e152 (2023). https://doi.org/10.1055/s-0043-1772607
5. Aja, P.M., Chiadikaobi, C.D., Agu, P.C., Ale, B.A., Ani, O.G., Ekpono, E.U., Ogwoni, H.A., Awoke, J.N., Ogbu, P.N., Aja, L., Nwite, F.E., Ukachi, O.U., Orji, O.U., Nweke, P.C., Egwu, C.O., Ekpono, E.U., Ewa, G.O., Igwenyi, I.O., Tusubira, D., Offor, C.E., Maduagwuna, E.K., Alum, E.U., Uti, D.E., Njoku, A., Atoki, V.A., Awuchi, C.G.: Cucumeropsis mannii seed oil ameliorates Bisphenol-A-induced adipokines dysfunctions and dyslipidemia. Food Sci Nutr. 11, 2642–2653 (2023). https://doi.org/10.1002/fsn3.3271
6. Rivera-Íñiguez, I., González-Becerra, K., Ramos-Lopez, O., Peréz-Beltrán, Y.E., Chagüén-Hernández, M.S., Martínez-López, E., Mendivil, E.J.: Lipid-Related Genetic Variants for Personalized Dietary Interventions: A Systematic Review. Mol Nutr Food Res. 67, e2200675 (2023). https://doi.org/10.1002/mnfr.202200675
7. Kirillova, O.: [Modern concepts of gene polymorphisms, which regulate lipid metabolism]. Voprosy pitaniia. (2012)
8. Sethupathy, P.: Needles in the genetic haystack of lipid disorders: single nucleotide polymorphisms in the microRNA regulome. Journal of Lipid Research. 54, 1168–1173 (2013). https://doi.org/10.1194/jlr.R035766
9. De Almeida, E.R.D., Reiche, E.M.V., Kallaur, A.P., Flauzino, T., Watanabe, M.A.E.: The Roles of Genetic Polymorphisms and Human Immunodeficiency Virus Infection in Lipid Metabolism. BioMed Research International. 2013, 1–15 (2013). https://doi.org/10.1155/2013/836790
10. Phillips, M.C.: Apolipoprotein E isoforms and lipoprotein metabolism. IUBMB Life. 66, 616–623(2014). https://doi.org/10.1002/iub.1314
11. Bennet, A.M., Di Angelantonio, E., Ye, Z., Wensley, F., Dahlin, A., Ahlbom, A., Keavney, B., Collins, R., Wiman, B., De Faire, U., Danesh, J.: Association of Apolipoprotein E Genotypes with Lipid Levels and Coronary Risk. JAMA. 298, 1300 (2007). https://doi.org/10.1001/jama.298.11.1300
12. Davignon, J., Gregg, R.E., Sing, C.F.: Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis. 8, 1–21 (1988). https://doi.org/10.1161/01.ATV.8.1.1
13. Eichner, J.E.: Apolipoprotein E Polymorphism and Cardiovascular Disease: A HuGE Review. American Journal of

Epidemiology. 155, 487–495 (2002). https://doi.org/10.1093/aje/155.6.487
14. Martínez-Magaña, J.J., Genis-Mendoza, A.D., Tovilla-Zarate, C.A., González-Castro, T.B., Juárez-Rojop, I.E., Hernández-Díaz, Y., Martinez-Hernandez, A.G., Garcia-Ortíz, H., Orozco, L., López-Narvaez, M.L., Nicolini, H.: Association between APOE polymorphisms and lipid profile in Mexican Amerindian population. Molecular Genetics & Genomic Medicine. 7, e958 (2019). https://doi.org/10.1002/mgg3.958
15. Husain, M.A., Laurent, B., Plourde, M.: APOE and Alzheimer's Disease: From Lipid Transport to Physiopathology and Therapeutics. Frontiers in Neuroscience. 15, 630502 (2021). https://doi.org/10.3389/fnins.2021.630502
16. Torres-Valadez, R., Ramos-Lopez, O., Delgadillo, K.J.F., Flores-García, A., Carrillo, E.R., Aguiar-García, P., Pérez, J.A.B., Martinez-Lopez, E., Martínez, J.A., Zepeda-Carrillo, E.A.: Impact of APOE Alleles-by-Diet Interactions on Glycemic and Lipid Features– A Cross-Sectional Study of a Cohort of Type 2 Diabetes Patients from Western Mexico: Implications for Personalized Medicine. Pharmacogenomics and Personalized Medicine. 13, 655 (2020). https://doi.org/10.2147/PGPM.S277952
17. Lozano, S., Padilla, V., Avila, M.L., Gil, M., Maestre, G., Wang, K., Xu, C.: APOE Gene Associated with Cholesterol-Related Traits in the Hispanic Population. Genes. 12, 1768 (2021). https://doi.org/10.3390/genes12111768
18. Rafaqat, S., Rafaqat, S., Sharif, S., Klisić, A.: Role of lipoprotein lipase variants in metabolic disorders and cardiovascular diseases. Arhiv za farmaciju. 74, 38–55 (2024). https://doi.org/10.5937/arhfarm74-48070
19. Jemaa, R., Tuzet, S., Portos, C., Betoulle, D., Apfelbaum, M., Fumeron, F.: Lipoprotein lipase gene polymorphisms: associations with hypertriglyceridemia and body mass index in obese people. International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity. (1995)
20. Ayyappa, K.A., Shatwan, I., Bodhini, D., Bramwell, L.R., Ramya, K., Sudha, V., Anjana, R.M., Lovegrove, J.A., Mohan, V., Radha, V., Vimaleswaran, K.S.: High fat diet modifies the association of lipoprotein lipase gene polymorphism with high density lipoprotein cholesterol in an Asian Indian population. Nutrition & Metabolism. 14, 8 (2017). https://doi.org/10.1186/s12986-016-0155-1
21. Pérez-Beltrán, Y.E., Rivera-Iñiguez, I., Gonzalez-Becerra, K., Pérez-Naitoh, N., Tovar, J., Sáyago-Ayerdi, S.G., Mendivil, E.J.: Personalized Dietary Recommendations Based on Lipid-Related Genetic Variants: A Systematic Review. Front. Nutr. 9, (2022). https://doi.org/10.3389/fnut.2022.830283
22. Xia, X., Peng, Z., Gu, H., Wang, M., Wang, G., Zhang, D.: Regulation of PCSK9 Expression and Function: Mechanisms and Therapeutic Implications. Frontiers in Cardiovascular Medicine. 8, 764038 (2021). https://doi.org/10.3389/fcvm.2021.764038
23. Glerup, S., Schulz, R., Laufs, U., Schlüter, K.-D.: Physiological and therapeutic regulation of PCSK9 activity in cardiovascular disease. Basic Res Cardiol. 112, 32 (2017). https://doi.org/10.1007/s00395-017-0619-0
24. Kaddoura, R., Orabi, B., Salam, A.M.: PCSK9 Monoclonal Antibodies: An Overview. Heart Views: The Official Journal of the Gulf Heart Association. 21, 97 (2020). https://doi.org/10.4103/HEARTVIEWS.HEARTVIEWS_20_20
25. Huang, C., Chen, W., Wang, X.: Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. Genes & Diseases. 10, 2351 (2022). https://doi.org/10.1016/j.gendis.2022.04.014
26. Oestereich, F., Yousefpour, N., Yang, E., Phénix, J., Nezhad, Z.S., Nitu, A., Cobá, A.V., Ribeiro-da-Silva, A., Chaurand, P., Munter, L.M.: The cholesteryl ester transfer protein (CETP) raises cholesterol levels in the brain. Journal of Lipid Research. 63, 100260 (2022). https://doi.org/10.1016/j.jlr.2022.100260
27. Smathers, R.L., Petersen, D.R.: The human fatty acid-binding protein family: Evolutionary divergences and functions. Human Genomics. 5, 170 (2011). https://doi.org/10.1186/1479-7364-5-3-170
28. Flores-Dorantes, M.T., Díaz-López, Y.E., Gutiérrez-Aguilar, R.: Environment and Gene Association with Obesity and Their Impact on Neurodegenerative and Neurodevelopmental Diseases. Frontiers in Neuroscience. 14, 863 (2020). https://doi.org/10.3389/fnins.2020.00863

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