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THE ATP-BINDING CASSETTE TRANSPORTER A1 GENE POLYMORPHISMS AND TYPE 2 DIABETES MELLITUS

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ABSTRACT

Insulin resistance (IR), secretion of insulin, and abnormalities of lipid metabolism are all markers of type 2 diabetes (T2DM), which is a progressive and complex metabolic disorder. Major risk factors for the development of T2DM were identified as genetic, environmental, and lifestyle factors. Several studies found that many genes contribute to T2DM susceptibility after glucose tolerance. Adenosine Binding Cassette Transporter Proteins 1 is a member of the ABC gene superfamily that is involved in cholesterol transport and HDL cholesterol (HDL-C) biosynthesis. Abnormal cholesterol metabolism, particularly high-density lipoprotein, has been related to genetic variations in the ABCA1 gene (HDL-C). Previous research suggested that ABCA1 gene polymorphisms may a hereditary risk factor for type 2 diabetes, along with lower HDL levels in various populations.

KEYWORDS: T2DM, ABCA1 gene, Genetic variations, SNPs

DIABETES MELLITUS

Diabetes mellitus is among the most prevalent chronic diseases worldwide. Hyperglycemia characterizes this metabolic disorder due to insulin insensitivity or insufficient levels. Long-term complications caused by Diabetic Mellitus are death and damage to different organs (1, 2). Diabetes currently affects 422 million people worldwide. This number is expected to increase to million by 2040 (http://www.diabetesatlas.org) (3).

Type two diabetes (T2DM) is a type of diabetes caused by insulin resistance or insufficiency. Monozygotic twins are more likely to be identical than dizygotic twins. Genetic and environmental conditions that affect beta-cell function and structure, resulting in altered tissue sensitivity to insulin, were found to play a significant role in Type 2 Diabetes Mellitus (T2DM). Cigarette smoking, lack of activity, low physical activity, poor diet, being overweight, and eating sugary foods all play a role in the progression of that disorder (4-6).

ATP-BINDING CASSETTE TRANSPORTER A1 (ABCA1) TRANSPORTER PROTEIN

The ABCA1 genes have been identified in 1994 as a novel subclass A member of the ABC superfamily. ABCA1 is a 149-kb gene on chromosome 9 (q31) that encodes a 240-kDa integral membrane protein with 2,261 amino acids (7). This protein forms an ATPase-dependent channel that transports lipids across the membrane (8). Cholesterol, phospholipids, and other lipophilic molecules are carried across the cell membrane through this channel.

The ATP-Binding Cassette Transporter A1 (ABCA1) is a symmetrical carrier with two transmembrane domains and two nucleotide binding domains (9, 10). Tangier disease is caused by mutations in the ABCA1 gene and has a genetic pattern characterized by autosomal dominance. Low HDL cholesterol levels in the blood and an accumulation of cholesteryl esters in the tissues are the characteristics of this disease (11). ABCA1 maintains intracellular cholesterol levels by removing excess cholesterol from cells (12). This lipid transporter is overexpressed in hepatocytes and non-hepatocytes, in accordance with its physiological function in these cells. To generate pre-HDL, ABCA1 transports all phospholipids and cholesterol from the cell to a lipid-free or lipid-poor apoA-I cell (13-17). ABCA1 is required for insulin secretion in beta cells; genetic changes in the ABCA1 gene disrupt high-density lipoprotein (HDL) metabolism, resulting in HDL deficiency (18). Cholesterol toxicity impairs beta cells' ability to secrete plasma and insulin, leading to

an increased risk of cardiovascular disorder and type-2 diabetes (19).

ABCA1 VARIANTS ARE ASSOCIATED WITH AN INCREASED RISK OF TYPE 2 DIABETES MELLITUS

The Gene for the ATP-Binding Cassette Transporter A1 (ABCA1) contains at least 50 exons with lengths ranging from 33 to 245 bp (20). The ABCA1 gene has over 70 rare mutations, mostly in the apoA-I binding site. These uncommon and common variants may contribute to susceptibility to type 2 diabetes. They prevent the transporter from maturing and the protein from binding to ApoA-I. Individuals with ABCA1 SNPs may have lower high-density lipoprotein (HDL) or ApoA-I levels in their plasma (21).

Several researches have established the effect of these gene changes located in the exons, promoter, introns, and 3' untranslated area on transporter function and structure, thereby contributing to the emergence of Type-2 diabetes and its complications (ABCA1 Genetic variants and Type 2 Diabetes Mellitus and Its Health problems) (18).

THE PROMOTER REGION OF RS1800977 (C69T) GENETIC POLYMORPHISM

Gene polymorphisms near the regulatory components of the ATP-Binding Cassette Transporter A1 Gene (ABCA1) proximal promoter area is related with an increased risk of developing more extreme hypertension (22). In this way, this variant of ABCA1 may play a central role in regulating the transcription of cholesterol trafficking, alone or in conjunction with several other genetic variations within the same gene or even other associated genes (23). A possible association between rs1800977 C69T variant and susceptibility to type 2 diabetes developments has also been described in various populations (24-27). The rs1800977 T allele and TT genotype, each thought to play a protective effect against T2DM, has been observed to be more prevalent in the subject of Turkey (25). A parallel result for the T allele has been demonstrated in a Saudi residents (26). As well as in the Malaysian residents (27). In individuals with and without prior myocardial injury, there is a significant association between the TT genotype and incidence of myocardial injury (24).

In a meta-analysis of the data from three eligible intervention studies, this polymorphism was suggested not to significantly impact the development of T2DM (25-27).

Cardiovascular disease account for the great majority of deaths among diabetics. High cholesterol and blood sugar levels in T2DM patients can result in blood vessel obstruction, atherosclerosis, and cerebral infarction (28-30). HDL receptor ABCA1 is essential in the metabolism of HDL. Decreased plasma HDL-C levels have been connected to, and the ABCA1 transporter in the surface of blood vessel cells, where HDL helps extracts cholesterol particles from the extracellular space, can contribute to severe atherosclerosis. Thus, this transporter plays a protective role in aortic atherosclerosis (31-33).

The patient with diabetes has a more risk of atherosclerosis, cardiovascular disease, since their lowered HDL concentrations. Patients suffering from Type 2 diabetes have lipid profiles that are not normal, making them more prone to heart disease and cerebral infarction (34). The results of a national study in Japan that included 3432 diabetes and non-diabetic cerebrovascular disease, as well as 2070 healthy controls (adjusted for gender, hypertension, diabetes, and hypercholesterolemia) indicate that the T allele variant of the rs1800977 gene is a potential risk for atherothrombotic cerebral infarction (35).

The role of the rs1800977 is not to act alone. It must work with additional SNPs in the ABCA1 or with other genes to do its job. The population subgroup with the HMGCR rs3931914 profile and the MTHFR rs1800977 and ApoE rs2422493 SNPs was identified as one of the potential risks for Alzheimer's disease in Spain (36). In accordance with the findings of a study conducted in non-diabetic Dutch people with CHD, the rs1800977 polymorphism cooperates with the rs2422493, rs1800976, and rs2740483 polymorphisms that cause the ABCA1 gene (37). In addition, Rs1800977 interacts with 3-hydroxy-3-methylglutaryl-CoA gene polymorphisms (HMGCR). This enzyme converts HMG-CoA to mevalonic acid, which is important in cholesterol synthesis. Then, the cholesterol is secreted by the ABCA1 transporter. A combination of poor ABCA1 expression and over-expression of HMGCR causes an increase in cholesterol levels in the plasma and brain, resulting in atherosclerosis and Alzheimer's disease (38, 39).

In the atherogenesis as a consequence of type 2 diabetes, the role of rs1800977 in the ABCA1 promoter or other areas of the ABCA1 gene remains unknown. Many studies have attempted to correlate rs1800977 to lipid profiles (40). The greatest significant effects were observed in models that included age, the interaction of rs1800977 and rs708272, and the isomer of cholesteryl ester transfer protein (CETP). Cholesteryl esters are transported from HDL to other lipoproteins by this protein, which is essential for this process to take place (41).

THE EXONIC REGION OF RS9282541 (R230C) GENETIC POLYMORPHISM

Rs9282541 is a rare non-synonymous SNP identified in the ABCA1 gene. As a result, the ABCA1 structure and function may be affected by the mutation. The substitution of C for T (CGT for TGT) results in the conversion of arginine to cysteine at the ABCA1 transporter's ED1 (23, 26). ApoA-I is triggered on the cell surface of the endoplasmic reticulum by directly interacting with the putative binding site in the ED-1 and ED-4 to stimulate ATP hydrolysis and subsequent cholesterol efflux from the ER (42). Clues that mutations in the ABCA1 transporter and ABCA1 stability sites are possible can lead to cellular lipid translocation deficits (43). ABCA1 is the gene that determines HDL levels. The rs9282541 gene, on the other hand, is associated with vulnerability to T2DM or high HDL levels in Mexican patients, but not in Colombians (18, 27, 44-47). The Mexican CT carriers were more likely to get T2DM early(44).

Other studies on the rs9282541 polymorphism have found no significant association with type 2 diabetes (27, 44, 46, 48). The rs9282541 is attributed to low HDL and high triglyceride levels and also with obesity risk. The CT/TT carriers had higher values of the HDL-3a/HDL-3b ratio as compared to the CC carriers (49-51). Flores-Dorantes et al. showed that this variation decreases HDL levels as a result of the gender-BMI interaction. Also, the examination of gender and genotype showed that men and CT carriers had the highest effect sizes(49).

Acua- Alonzo et al. discovered that Native Americans have a greater prevalence of the allele TT at the rs9282541 locus, indicating a potential selective advantage for higher HDL levels and other metabolic features. In this population, decreased HDL-C levels were found to be associated with a higher BMI. In vitro study revealed that the A allele resulted in a 27% decrease in cholesterol efflux. This finding shows how this protein shows functionality in this study (52). As a result, the rs9282541 T allele could be a key factor in spreading this ethnic group's resistance to metabolic diseases (52). However, another study did not support the use of traditional markers in admixture mapping. Evaluation of genome regions in the subject showed no deviation from the Native American genome. The researchers propose that socioeconomic status is a useful indicator of T2DM within that ethnicity(47).

Previous research has shown a correlation between rs9282541 and lifestyle factors. The association of rs9282541 with dietary carbohydrate and fat intake, gamma-glutamyl transpeptidase, alkaline phosphatase, adiponectin, and insulin resistance may lower HDL levels in Mexicans (10, 53). Individuals with CT genotypes reacted better to dietary pattern treatment with soy protein, nopal, oat, and chia seed than those with TT genotypes. There was an even stronger therapeutic impact seen with more metabolic syndrome individuals(54, 55).

THE EXONIC REGION OF RS2230806 (R219K) GENETIC POLYMORPHISM

There is a mutation in the ABCA1 gene called rs2230806. This mutation is in exon 7. There are two types of polymorphisms in this gene: one that changes the amino acid arginine to lysine (R219K) and one that changes a G nucleotide to an A nucleotide. It has a beneficial effect on the structure and stability of proteins (12, 23). The rs2230806 is associated with high high-density lipoprotein levels related to type 2 diabetes(56, 57). HDL-C, which is in our bloodstream, directly regulates the plasma's glucose concentration by stimulating insulin secretion by our pancreas and altering glucose uptake in our skeletal muscles(58).

Researchers found a possible correlation between a particular risk allele on an AA genotype and higher high-density lipoprotein levels in Asians (57). A study in Malaysia has shown that A allele and AA genotype carriers are more suitable for T2DM than alternative alleles or genotypes. This finding has been supported by Haghvirdizadeh et al (27). The low incidence of A allele was also found in diabetes patients with previous coronary heart disease –(24).

In a study of Type 2 diabetes patients, the gene rs2230806 was also found to increase the chances of responding well to a drug that lowers blood sugar levels. Specifically, in Type 2 diabetes patients, the rs2230806 was associated with the antidiabetic drug response, rosiglitazone (59). ABCA1 is a highly expressed protein in the mouse pancreatic beta cells. Deficiency in this specific transporter results in cellular cholesterol accumulation and reduces insulin secretion. This results in a progressive impairment in glycaemic control. Rosiglitazone increased insulin sensitivity in the mice with T2DM by enhancing the expression of ABCA1 (60). In Chinese ethnicities, carriers of the r2 allele of rs2230806 have a stronger response to rosiglitazone than carriers of the A allele(61).

Other researchers showed that the A allele variant plays a protective effect against atherosclerosis (61), Coronary heart disease (CHD) (62), and ischemic stroke (63), but doesn't in Alzheimer's disease (AD) '(64, 65).

Studies show that high HDL levels decrease atherosclerosis chances by increasing the endothelium's oxidation and restoration and by

exerting anti-inflammation and anti-apoptotic effects (65). Other studies showed that low levels of High-Density Lipoprotein (HDL) are closely associated with disease progression of Type 2 Diabetes Mellitus (T2DM) (66). They may accelerate and promote atherosclerosis, myocardial infarction, and Coronary heart disease (CHD). The rs2230806 is strongly correlated with serum high-density lipoprotein (HDL) levels and response to antidiabetic drugs in T2DM (67). The ABCA1 is an efflux transporter that is critical for regulating HDL function and cholesterol homeostasis in the body; identifying the ABCA1 gene and its monogenic mutations has become a new strategy for earlier diagnosis and prognosis of 2 diabetes(68).

CONCLUSION

A number of studies have shown that having the ABCA1 gene polymorphism may increase one's threat of developing type 2 diabetes and its complications, and also conditions that contribute to the development of type 2 diabetes, such as lower serum high-density lipoprotein (HDL) levels type 2 diabetes and/or heart disease (CHD) (69). To recognize and better understand the role of these SNPs, we summarized the existing evidence by focusing more on rs2230806 (R219K), rs1800977 (C69T), and rs9282541 (R230C) variants. Specific variants are associated with reduced cholesterol efflux, This raises the risk for type 2 diabetes and its consequences and the medication's responsiveness in the patients.

REFERENCES

1. Nathan DM. Long-term complications of diabetes mellitus. New England Journal of Medicine. 1993;328(23):1676-85.
2. Piero M, Nzaro G, Njagi J. Diabetes mellitus-a devastating metabolic disorder. Asian journal of biomedical and pharmaceutical sciences. 2015;5(40):1.
3. ATLAS I. 2017: http://www. diabetesatlas. org. Accessed on Feb 10th. 2019.
4. Dong Y, Wu Y, Choi HC, et al. Diabetic endothelium dysfunction, cardiovascular complications, and therapeutics. Hindawi; 2016.
5. Cameron A, Zimmet P, Soderberg S, et al. The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius. Diabetic medicine. 2007;24(12):1460-9.
6. Hansen T, editor Type 2 diabetes mellitus--a multifactorial disease. Annales Universitatis Mariae Curie-Sklodowska Sectio D: Medicina; 2002.
7. Plengvidhya N, Boonyasrisawat W, Jungtrakoon P, Sujjitjoon J, et al. Molecular genetics of diabetes mellitus. Siriraj Medical Journal. 2008;60(5):273-8.
8. Kaminski WE, Piehler A, Wenzel JJ. ABC A-subfamily transporters: structure, function and disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2006;1762(5):510-24.
9. Schmitz G, Buechler C. ABCA1: regulation, trafficking and association with heteromeric proteins. Annals of medicine. 2002;34(5):334-47.
10. Aguilar Salinas CA, Cruz-Bautista I, Mehta R, et al. The ATP-binding cassette transporter subfamily A member 1 (ABC-A1) and type 2 diabetes: an association beyond HDL cholesterol. Current diabetes reviews. 2007;3(4):264-7.
11. Puntoni M, Sbrana F, Bigazzi F, et al. Tangier disease. American Journal of Cardiovascular Drugs. 2012;12(5):303-11.
12. Oram JF, Heinecke JW. ATP-binding cassette transporter A1: a cell cholesterol exporter that protects against cardiovascular disease. Physiological reviews. 2005;85(4):1343-72.
13. Poitout V, Robertson RP. Minireview: secondary β-cell failure in type 2 diabetes—a convergence of glucotoxicity and lipotoxicity. Endocrinology. 2002;143(2):339-42.
14. Ye D, Lammers B, Zhao Y, et al. ATP-binding cassette transporters A1 and G1, HDL metabolism, cholesterol efflux, and inflammation: important targets for the treatment of atherosclerosis. Current drug targets. 2011;12(5):647-60.
15. Oram JF. HDL apolipoproteins and ABCA1: partners in the removal of excess cellular cholesterol. Arteriosclerosis, thrombosis, and vascular biology. 2003;23(5):720-7.
16. Zhao G-J, Yin K, Fu Y-c, et al. The interaction of ApoA-I and ABCA1 triggers signal transduction pathways to mediate efflux of cellular lipids. Molecular medicine. 2012;18(2):149-58.
17. Huang C-X, Zhang Y-L. The target of regulating the ATP-binding cassette A1 protein (ABCA1): promoting ABCA1-mediated cholesterol efflux in different cells. Current Pharmaceutical Biotechnology. 2013;14(6):623-31.
18. Haerian BS, Haerian MS, Roohi A, et al. ABCA1 genetic polymorphisms and type 2 diabetes mellitus and its complications. Meta Gene. 2017;13:104-14.

19. Bardini G, Rotella CM, Giannini S. Dyslipidemia and diabetes: reciprocal impact of impaired lipid metabolism and Beta-cell dysfunction on micro- and macrovascular complications. The review of diabetic studies: RDS. 2012;9(2-3):82.
20. Santamarina-Fojo S, Peterson K, Knapper C, et al. Complete genomic sequence of the human ABCA1 gene: analysis of the human and mouse ATP-binding cassette A promoter. Proceedings of the National Academy of Sciences. 2000;97(14):7987-92.
21. Willer CJ, Sanna S, Jackson AU, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nature genetics. 2008;40(2):161-9.
22. Yamada Y, Kato K, Yoshida T, et al. Association of polymorphisms of ABCA1 and ROS1 with hypertension in Japanese individuals. International journal of molecular medicine. 2008;21(1):83-9.
23. Brunham LR, Singaraja RR, Pape TD, et al. Accurate prediction of the functional significance of single nucleotide polymorphisms and mutations in the ABCA1 gene. PLoS Genet. 2005;1(6):e83.
24. Porchay-Baldérelli I, Péan F, Emery N, Maimaitiming S, et al. Relationships between common polymorphisms of adenosine triphosphate–binding cassette transporter A1 and high-density lipoprotein cholesterol and coronary heart disease in a population with type 2 diabetes mellitus. Metabolism. 2009;58(1):74-9.
25. Ergen HA, Zeybek Ü, Gök Ö, et al. Investigation of ABCA1 C69T polymorphism in patients with type 2 diabetes mellitus. Biochemia medica: Biochemia medica. 2012;22(1):114-20.
26. Alharbi KK, Khan IA, Al-Daghri NM, et al. ABCA1 C69T gene polymorphism and risk of type 2 diabetes mellitus in a Saudi population. Journal of biosciences. 2013;38(5):893-7.
27. Haghvirdizadeh P, Ramachandran V, Etemad A, Heidari F, et al. Association of ATP-binding cassette transporter A1 gene polymorphisms in type 2 diabetes mellitus among Malaysians. Journal of diabetes research. 2015;2015.
28. Group NDD, Diabetes NIo, Digestive, Diseases K. Diabetes in America: National Institutes of Health, National Institute of Diabetes and Digestive …; 1995.
29. Arboix A, Rivas A, García-Eroles L, et al. Cerebral infarction in diabetes: clinical pattern, stroke subtypes, and predictors of in-hospital mortality. BMC neurology. 2005;5(1):9.
30. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Physical therapy. 2008;88(11):1254-64.
31. Aguilar-Salinas CA, Rojas R, Gómez-Pérez FJ, et al. High prevalence of metabolic syndrome in Mexico. Archives of medical research. 2004;35(1):76-81.
32. Hovingh GK, van Wijland MJ, Brownlie A, et al. The role of the ABCA1 transporter and cholesterol efflux in familial hypoalphalipo proteinemia. Journal of lipid research. 2003;44 (6):1251-5.
33. Tan JH-H, Low P-S, Tan Y-S, et al. ABCA1 gene polymorphisms and their associations with coronary artery disease and plasma lipids in males from three ethnic populations in Singapore. Human genetics. 2003;113(2):106-17.
34. Ozder A. Lipid profile abnormalities seen in T2DM patients in primary healthcare in Turkey: a cross-sectional study. Lipids in health and disease. 2014;13(1):183.
35. Yamada Y, Metoki N, Yoshida H,et al. Genetic factors for ischemic and hemorrhagic stroke in Japanese individuals. Stroke. 2008;39(8):2211-8.
36. Rodríguez-Rodríguez E, Mateo I, Infante J, Llorca J, et al. Interaction between HMGCR and ABCA1 cholesterol-related genes modulates Alzheimer's disease risk. Brain research. 2009;1280:166-71.
37. Regieli JJ, Doevendans PA, Grobbee DE, et al. ABCA1 impacts athero-thrombotic risk and 10-year survival in a contemporary secondary prevention setting. Atherosclerosis. 2011;218(2):457-63.
38. Owens D, Collins P, Johnson A, et al. Hypercholesterolaemia: simvastatin and pravastatin alter cholesterol metabolism by different mechanisms. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism. 1991;1082(3):303-9.
39. Kessler E, Gross JJ, Bruckmaier R, et al. Cholesterol metabolism, transport, and hepatic regulation in dairy cows during transition and early lactation. Journal of Dairy Science. 2014;97(9):5481-90.
40. White MJ, Eren F, Ağırbaşlı D, et al. A systems genetics approach to dyslipidemia in children and adolescents. OMICS: A Journal of Integrative

Biology. 2015;19(4):248-59.

41. Kardassis D, Mosialou I, Kanaki M, et al. Metabolism of HDL and its regulation. Current medicinal chemistry. 2014;21(25):2864-80.
42. Yokoyama S. Apolipoprotein-mediated cellular cholesterol efflux. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism. 1998;1392(1):1-15.
43. Wang S, Smith JD. ABCA1 and nascent HDL biogenesis. Biofactors. 2014;40(6):547-54.
44. Villarreal-Molina MT, Flores-Dorantes MT, Arellano-Campos O, et al. Association of the ATP-binding cassette transporter A1 R230C variant with early-onset type 2 diabetes in a Mexican population. Diabetes. 2008;57(2):509-13.
45. Arjona Villicaña RD, Melgarejo Hernández MA, Hernández Alarcón J, et al. The ATP-binding cassette transporter a1 R230C variant does not modify the weight loss response to hypocaloric diet. Revista mexicana de endocrinología metabolismo & nutrición. 2015;2(3):128-37.
46. Lara-Riegos J, Ortiz-López M, Peña-Espinoza B, et al. Diabetes susceptibility in Mayas: evidence for the involvement of polymorphisms in HHEX, HNF4α, KCNJ11, PPARγ, CDKN2A/2B, SLC30A8, CDC123/CAMK1D, TCF7L2, ABCA1 and SLC16A11 genes. Gene. 2015;565 (1):68-75.
47. Campbell DD, Parra MV, Duque C, et al. Amerind ancestry, socioeconomic status and the genetics of type 2 diabetes in a Colombian population. Plos one. 2012;7(4):e33570.
48. Miranda-Lora AL, Cruz M, Aguirre-Hernández J, et al. Exploring single nucleotide polymorphisms previously related to obesity and metabolic traits in pediatric-onset type 2 diabetes. Acta Diabetologica. 2017;54(7):653-62.
49. Flores-Dorantes T, Arellano-Campos O, Posadas-Sánchez R, et al. Association of R230C ABCA1 gene variant with low HDL-C levels and abnormal HDL subclass distribution in Mexican school-aged children. Clinica Chimica Acta. 2010;411(17-18):1214-7.
50. Aguilar-Salinas CA, Canizales-Quinteros S, Rojas-Martínez R, et al. The non-synonymous Arg230Cys variant (R230C) of the ATP-binding cassette transporter A1 is associated with low HDL cholesterol concentrations in Mexican adults: a population based nation wide study. Atherosclerosis. 2011;216(1):146-50.
51. Gamboa-Meléndez MA, Galindo-Gómez C, Juárez-Martínez L, et al. Novel association of the R230C variant of the ABCA1 gene with high triglyceride levels and low high-density lipoprotein cholesterol levels in Mexican school-age children with high prevalence of obesity. Archives of medical research. 2015;46(6):495-501.
52. Acuña-Alonzo V, Flores-Dorantes T, Kruit JK, et al. A functional ABCA1 gene variant is associated with low HDL-cholesterol levels and shows evidence of positive selection in Native Americans. Human Molecular Genetics. 2010;19(14):2877-85.
53. Jacobo-Albavera L, Posadas-Romero C, Vargas-Alarcón G, et al. Dietary fat and carbohydrate modulate the effect of the ATP-binding cassette A1 (ABCA1) R230C variant on metabolic risk parameters in premenopausal women from the Genetics of Atherosclerotic Disease (GEA) Study. Nutrition & metabolism. 2015;12(1):45.
54. Guevara-Cruz M, Tovar AR, Larrieta E, et al. Increase in HDL-C concentration by a dietary portfolio with soy protein and soluble fiber is associated with the presence of the ABCA1R230C variant in hyperlipidemic Mexican subjects. Molecular genetics and metabolism. 2010;101(2-3):268-72.
55. Guevara-Cruz M, Tovar AR, Aguilar-Salinas CA, et al. A dietary pattern including nopal, chia seed, soy protein, and oat reduces serum triglycerides and glucose intolerance in patients with metabolic syndrome. The Journal of nutrition. 2012;142(1):64-9.
56. Ma X-y, Liu J-p, Song Z-y. Associations of the ATP-binding cassette transporter A1 R219K polymorphism with HDL-C level and coronary artery disease risk: a meta-analysis. Atherosclerosis. 2011;215(2):428-34.
57. Haase CL, Tybjærg-Hansen A, Nordestgaard BG, et al. HDL cholesterol and risk of type 2 diabetes: a Mendelian randomization study. Diabetes. 2015;64(9):3328-33.
58. Vergeer M, Brunham LR, Koetsveld J, et al. Carriers of loss-of-function mutations in ABCA1 display pancreatic β-cell dysfunction. Diabetes Care. 2010;33(4):869-74.
59. Wang J, BAO Yq, Hu C, Zhang R, et al. Effects of ABCA1 variants on rosiglitazone monotherapy in newly diagnosed type 2 diabetes patients 1. Acta pharmacologica Sinica. 2008;29(2):252-8.
60. Brunham LR, Kruit JK, Verchere CB, et al..

Cholesterol in islet dysfunction and type 2 diabetes. The Journal of clinical investigation. 2008;118(2):403-8.

61. Yin Y-W, Li J-C, Gao D, et al. Influence of ATP-binding cassette transporter 1 R219K and M883I polymorphisms on development of atherosclerosis: a meta-analysis of 58 studies. PLoS One. 2014;9(1):e86480.
62. Li J-F, Peng D-Y, Ling M, et al.. Evaluation of adenosine triphosphate-binding cassette transporter A1 (ABCA1) R219K and C-reactive protein gene (CRP)+ 1059G/C gene polymorphisms in susceptibility to coronary heart disease. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2016;22:2999.
63. Jiang M, Lv L, Wang H, et al. Meta-analysis on association between the ATP-binding cassette transporter A1 gene (ABCA1) and Alzheimer's disease. Gene. 2012;510(2):147-53.
64. Wang X-F, Cao Y-W, Feng Z-Z, et al. Quantitative assessment of the effect of ABCA1 gene polymorphism on the risk of Alzheimer's disease. Molecular biology reports. 2013;40(2):779-85.
65. Rosenson RS, Brewer HB, Ansell BJ, et al. Dysfunctional HDL and atherosclerotic cardiovascular disease. Nature reviews cardiology. 2016;13(1):48-60.
66. Kruit JK, Brunham LR, Verchere CB, et al. HDL and LDL cholesterol significantly influence β-cell function in type 2 diabetes mellitus. Current opinion in lipidology. 2010;21(3):178-85.
67. Shah MS, Brownlee M. Molecular and cellular mechanisms of cardiovascular disorders in diabetes. Circulation research. 2016;118(11):1808-29.
68. Talbot CP, Plat J, Ritsch A, et al.. Determinants of cholesterol efflux capacity in humans. Progress in lipid research. 2018;69:21-32.
69. Ouimet M, Barrett TJ, Fisher EA. HDL and reverse cholesterol transport: basic mechanisms and their roles in vascular health and disease. Circulation research. 2019;124(10):1505-18.

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