MONOGENIC DISORDERS ALTERING HDL LEVELS

Michael D. Shapiro, DO, MCR Professor of Cardiology and Molecular Medicine, Wake Forest University School of Medicine, Winston-Salem, N.C. mdshapir@wakehealth.edu

Kenneth R. Feingold MD, Kenneth R. Feingold, MD, received his medical degree from the State University of New York, Upstate Medical Center in Syracuse, New York. He completed his internship and residency in internal medicine at the University of Wisconsin in Madison, Wisconsin and a fellowship in endocrinology and metabolism at the University of California, San Francisco. He is currently an Emeritus Professor of Medicine in the Endocrinology Section at the University of California San Francisco. For many years he was Chief of the Endocrine Clinic at the San Francisco VA.

Received November 19, 2021

ABSTRACT

Very low HDL-C levels (<20mg/dL) may be due to severe elevations in triglycerides, very poorly controlled diabetes, inflammation, infections, malignancy, liver disease, and certain medications such as anabolic steroids. Additionally, variants in multiple genes that each have a small effect but cumulatively lead to a decrease in HDL-C can result in very low HDL-C levels. Finally, rare monogenic disorders such as familial hypoalphalipoproteinemia, Tangier disease, and lecithin acyltransferase (LCAT) deficiency can lead to very low HDL-C levels. In this chapter we discuss the lipid abnormalities and clinical features of these monogenic disorders causing very low HDL-C levels. An elevated concentration of apo A-I and apo A-II is called hyperalphalipoproteinemia (HALP). HALP is classified as moderate (HDL-C levels between 80 and 100 mg/dL) or severe (HDL-C levels > 100 mg/dL). HALP is a heterogeneous condition caused by a variety of genetic and secondary conditions (for example ethanol abuse, primary biliary cirrhosis, multiple lipomatosis, emphysema, exercise, and certain drugs such as estrogens). In many individuals HALP has a polygenic origin. Monogenic HALP includes CETP deficiency, hepatic lipase deficiency, endothelial lipase deficiency, and loss of function mutations in SRB1. In this chapter we discuss the lipid abnormalities and clinical features of these monogenic disorders causing HALP.

LOW HDL CONDITIONS

The inverse relationship between HDL-C and ASCVD risk is well established but it should be recognized that while this association is consistently observed recent genetic and cardiovascular outcome studies suggest that this association is not causal (1). However, as discussed below major reductions in HDL-C induced by monogenic disorders may increase the risk of ASCVD.

Isolated low HDL-C levels can occur; however, it is more commonly found in association with hypertriglyceridemia and/or elevated apo B levels, typically as part of the obesity/metabolic syndrome (2). Patients with very low HDL-C (<20 mg/dl) in the absence of severe hypertriglyceridemia, very poorly controlled diabetes, inflammation, infections, malignancy, liver disease, anabolic steroids, or a paradoxical response to PPAR agonists are very rare (<1% of the population) (3,4). These individuals may have a rare monogenic disorder associated with marked HDL deficiency, including familial hypoalphalipoproteinemia, Tangier disease, and lecithin acyltransferase (LCAT) deficiency. Table 1 summarizes the genetic, lipid, and clinical features of these monogenic low HDL conditions. In some individuals the decrease in HDL-C can be polygenic i.e., variants in multiple genes that each have a small effect but cumulatively lead to a decrease in HDL-C.

Table 1. Characteristics of Monogenic Low HDL Syndromes			
	Effected genes	**Lipids**	**Clinical features**
Familial hypoalpha-lipoproteinemia	apo A-I/apo C-III/ apo A-IV apo A-I/apo C-III apo A-I	Apo AI undetectable, marked deficiency in HDL-C, low – normal triglycerides, normal LDL-C	Xanthomas Premature ASCVD Corneal manifestations
Tangier disease	ABCA1	HDL species exclusively preß-1, HDL-C <5 mg/dl LDL-C low (half normal)	Hepatosplenomegaly Enlarged tonsils Neuropathy ASCVD (6-7th decade)
LCAT deficiency	LCAT	HDL-C <10 mg/dl apo A-I 20-30 mg/dl <36% cholesteryl esters Low LDL-C Presence of Lp-X particles	FLD develop corneal opacities ("fish eye"), normochromic anemia and proteinuric end stage renal disease FED only develop corneal opacities

Inheritance is autosomal co-dominant with heterozygotes having decreases in HDL-C levels approximately midway between normal and homozygotes (3). FLD- Familial Lecithin: Cholesteryl Ester Acyltransferase Deficiency; FED- Fish Eye Disease

Familial Hypoalphalipoproteinemia

Familial hypoalphalipoproteinemia is a heterogeneous group of apolipoprotein A-I (apo A-I) deficiency states. This disorder is the rarest cause of monogenic severe HDL deficiency (5). These various conditions are characterized by the specific apolipoprotein genes that are affected on the apo A-I/C-III/A-IV gene cluster (3). The genes for these 3 apolipoproteins (apo A-I, apo C-III, and apo A-IV) are grouped together in a cluster on human chromosome 11. In patients with apo A-I/C-III/A-IV deficiency, apoA-1 is undetectable in the plasma and is associated with marked deficiency in HDL-C, low triglyceride levels (due to apo C-III deficiency), and normal LDL-C levels (3). Heterozygotes have plasma HDL-C, apo A-I, apo A-IV, and apo C-III levels that are about 50% of normal (3). This condition is associated with aggressive, premature ASCVD. Additionally, there is evidence of mild fat malabsorption. Patients with apo A-I/C-III deficiency have undetectable apo A-I and a similar lipid profile as those with apo A-I/C-III/A-IV deficiency (3). This condition is also associated with premature ASCVD. It is distinguished from the former by presence of planar xanthomas and absence of fat malabsorption (since apo A-IV is present). Familial apo A-I deficiency is itself a heterogeneous group of disorders associated with numerous Apo A-I mutations (3). Common manifestations include undetectable plasma Apo A-I, marked HDL deficiency with normal LDL-C and triglyceride levels, xanthomas (planar, tendon, and/or tubero-eruptive depending on the specific gene mutation), and premature ASCVD. Some forms of the disease are also associated with corneal manifestations, including corneal arcus and corneal opacification. One of the interesting manifestations of familial apo A-I deficiency is that levels of apo A-IV and apo E containing HDL particles are only modestly reduced, with preserved electrophoretic mobility and particle size (6).

It is notable that familial hypoalphalipoproteinemia is associated with an increased risk of premature ASCVD presumably due to the marked deficiency in Apo A-I and HDL. Given the increased ASCVD risk associated with Apo A-I deficiency, treatment is directed towards aggressive reduction of LDL-C and non-HDL-C levels and reducing other cardiovascular risk factors.

Some mutations in Apo A-I are associated with low HDL-C levels and hereditary amyloidosis and are the second most frequent cause of familial amyloidosis (5). Note that HDL-C levels are not always decreased in patients with familial amyloidosis secondary to Apo A-I mutations. Mutations in the amino-terminal domain of Apo A-I are associated with hepatic and renal amyloidosis, whereas mutations affecting residues 173–178 are mostly responsible for cardiac, laryngeal, and cutaneous amyloidosis The N-terminal fragment of the mutated protein is found in the amyloid fragments.

Tangier Disease

Tangier disease is due to mutations in the gene that codes for ATP-Binding Cassette transporter A1 (ABCA1) and is inherited in an autosomal recessive manner (7,8). Fredrickson first reported this condition in two patients who hailed from Tangier Island in the Chesapeake Bay, for which the disorder is named. ABCA1 facilitates efflux of intracellular cholesterol from peripheral cells to lipid poor A1, the key first step of reverse cholesterol transport (9). As such, this disorder is characterized by severe deficiency of HDL-C (HDL-C <5 mg/dl) and the presence of only the preß-1 HDL fraction of HDL (8). The poorly lipidated Apo A-I is rapidly catabolized by the kidney. These patients also demonstrate moderate hypertriglyceridemia and low LDL-C levels (8). The decrease in LDL-C is likely due to absence of the transfer of cholesterol from HDL to LDL. Studies have also suggested that an increase in LDL uptake by the liver also occurs (10). The increase in triglycerides may be due to the failure of HDL to provide co-factors that increase lipoprotein lipase activity. Additionally, ABCA1 deficiency in the liver increases triglyceride secretion and hepatic angiopoietin-like protein 3 secretion which could inhibit lipoprotein lipase activity leading to an increase in triglycerides (10,11).

Since ABCA1 deficiency impairs free cholesterol efflux from cells, there is accumulation of cholesterol esters in many tissues throughout the body (8). Classically, patients present with hepatosplenomegaly and enlarged tonsils, however, a wide spectrum of phenotypic manifestations is now appreciated with considerable variability in terms of clinical severity and organ involvement (7,8). Peripheral neuropathies are also a common complication and may be relapsing-remitting or chronic progressive (7,8). Tangier disease patients appear to have an increased risk of premature ASCVD, though not as pronounced as those with familial hypoalphalipoproteinemia (3,7,12). When the non-HDL-C levels are greater than 70mg/dL patients with Tangier disease are at higher risk of ASCVD whereas when the non-HDL-C levels are less than 70mg/dL ASCVD is low (7). Less common complications include corneal opacities and hematological manifestations such as thrombocytopenia and hemolytic anemia (7,8).

Individuals who are heterozygous for ABCA1 mutations have HDL-C levels that are variable but approximately 50% of normal with normal levels of preß-1 HDL but a deficiency of large α-1 and α-2 HDL particles (8). Cholesterol efflux capacity in heterozygotes has been reported as ~50% of normal. A mutation in one ABCA1 allele has been associated with increased risk of ASCVD in some studies with no increase in ASCVD risk in other studies (13-18). Different mutations in ABCA1 result in varying HDL-C levels and phenotypes, which might explain the difference in ASCVD risk (19).

While Tangier patients manifest characteristically low HDL-C and Apo A-I, this lipid/lipoprotein phenotype is not adequate to make the diagnosis. ABCA1 gene sequence analysis is the preferred test to make the diagnosis of Tangier disease (8). Alternatively, non-denaturing two-dimensional electrophoresis followed by anti-apo A-I immunoblotting demonstrates only preβ1-HDL.

Currently, there is no specific treatment for Tangier disease (8). In fact, HDL-C raising therapies such as niacin and fibrates have proven ineffective in patients with this condition (20). Even HDL infusion was not beneficial (21). The major clinical issue in Tangier patients is disabling neuropathy; however, there is no effective intervention to manage this complication (8). Aggressive LDL-C lowering and treatment of other risk factors for atherosclerosis is recommended (8).

LCAT Deficiency

LCAT is an enzyme that is bound primarily to HDL, with some also found on LDL (22,23). It facilitates cholesterol esterification by transferring a fatty acid from phosphatidyl choline to cholesterol (22,23). The hydrophobic cholesteryl esters are then sequestered into the core of the lipoprotein

particles. LCAT is critical in the maturation of HDL particles. LCAT deficiency is an autosomal recessive disorder that manifests as either familial LCAT deficiency (FLD) or fish-eye disease (FED) (22,23). In FLD, mutations in LCAT lead to the inability of LCAT to esterify cholesterol in both HDL and LDL, whereas in FED, mutations in LCAT lead to the inability of LCAT to esterify cholesterol in HDL but the ability of LCAT to esterify cholesterol in LDL is preserved (22,23). Patients with FLD have virtually no cholesterol esters in the circulation while patients with FED have subnormal levels of cholesterol esters carried in apo B containing lipoproteins (22,23).

Individuals with FLD develop corneal opacities ("fish eye"), normochromic hemolytic anemia (due to cholesterol enrichment of red blood cell membranes), mild thrombocytopenia, and proteinuric end stage renal disease, which is the major cause of morbidity and mortality (22,23). The corneal opacities begin early in life and some patients may need corneal transplants. The rate of development of renal disease is variable but in a large cohort renal failure occurred at a median age of 46 years (24). Patients with FED generally only manifest the corneal opacities (22,23).

The lipid and lipoprotein profile in patients with FLD usually demonstrates low HDL-C levels (frequently <10 mg/dl) (22). In one cohort patients with FED tend to have higher HDL-C levels but in a large systematic review HDL-C levels were similar in patients with FLD and FED (22,25). LDL-C levels tend to be low in both FLD and FED while triglyceride levels are increased (22,25). Lipoprotein X (Lp-X) particles are present in patients with FLD but not in patients with FED (22). Lp-X is a multilamellar vesicle with an aqueous core. It is primarily composed of free cholesterol and phospholipid with very little protein (albumin in the core and apolipoprotein C on the surface) and cholesteryl ester.

Given the association of Lp-X and kidney disease only with FLD (and not FED) and animal studies demonstrating the nephrotoxicity of Lp-X, it is likely that increased levels of Lp-X results in renal dysfunction in patients with FLD (23,26). Lp-X particles accumulate in the mesangial cells in the glomerulus and are thought to induce inflammation and breakdown of the basement membrane leading to proteinuria. It is notable that after renal transplantation in patients with FLD there is recurrence of renal damage in the transplanted kidney (24).

It is unclear as to whether LCAT deficiency is associated with an increased risk of ASCVD (23,27). Atherosclerosis imaging studies have yielded divergent data and the number of patients with FLD or FED studied is limited (23,27).

Current management of FLD focuses on managing the renal dysfunction. The associated kidney disease is traditionally managed with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and a low-fat diet (23). Whether lipid lowering drugs are beneficial is unknown. Possible future therapies include enzyme replacement therapy with recombinant human LCAT, liver-directed LCAT gene therapy, and small peptide or molecule activators of LCAT (28). Infusions of recombinant human LCAT has improved the anemia and most parameters of renal function in a patient with FLD (29). Administration of CER-001, an apolipoprotein A1 (apoA-1)–containing HDL mimetic, has been shown to have beneficial effects on kidney and eye disease in a patient with LCAT deficiency (30).

Approach to the Patient with Low HDL Levels

When encountering a patient with very low HDL-C levels it is important to first determine if this is a new abnormality or has been present for a long time. If prior HDL-C levels are normal, this excludes a primary monogenic etiology. If the decrease in HDL-C is new, one should consider the possibility of very poorly controlled diabetes, inflammation, infections, malignancy, liver disease, paraproteinemia, anabolic steroids, or a paradoxical response to PPAR agonists. Marked hypertriglyceridemia can also lead to very low HDL-C levels.

In a patient with long-standing very low HDL-C levels without an identifiable secondary cause, one should consider a monogenic etiology. To evaluate potential monogenic causes, a detailed family history, with attention to HDL-C levels, is important. Obtaining lipid levels from relatives is very helpful. A focused physical examination, with particular attention to the skin, eyes, tonsils, and spleen may point to a specific monogenic disorder. Plasma apo A-I levels should be obtained. Individuals with apo A-I deficiency have undetectable plasma apo A-I. Patients

with Tangier disease demonstrate very low apo A-I levels (<5 mg/dl). LCAT deficiency is associated with apo A-I levels that are low but substantially higher than the other monogenic etiologies. Patients with LCAT deficiency also have a higher ratio of free: total cholesterol in plasma and measurement of plasma free (unesterified) cholesterol can be helpful. Two-dimensional gel electrophoresis of plasma followed by immunoblotting with antibodies specific for apo A-I separates lipid-poor preß-HDL from lipid-rich–HDL and can be helpful in differentiating these disorders. Genetic analysis is indicated when a monogenic disorder is suspected. Note in some individuals the decrease in HDL-C can be polygenic.

HIGH HDL CONDITIONS (HYPERALPHALIPOPROTEINEMIA)

An elevated concentration of apo A-I and apo A-II is called hyperalphalipoproteinemia (HALP). HALP is classified as moderate (HDL-C levels between 80 and 100 mg/dL) or severe (HDL-C levels > 100 mg/dL). HALP is a heterogeneous condition caused by a variety of genetic and secondary conditions (for example ethanol abuse, primary biliary cirrhosis, multiple lipomatosis, emphysema, exercise, and certain drugs such as estrogens). In many individuals, the very high HDL-C levels have a polygenic origin (31,32). Given the focus of this chapter, monogenic causes of HALP will be reviewed. Monogenic HALP includes CETP deficiency, hepatic lipase deficiency, endothelial lipase deficiency, and loss of function mutations in SRB1. Despite the consistent epidemiology that demonstrates an inverse relationship between HDL-C and ASCVD risk, some forms of familial HALP are paradoxically associated with increased cardiovascular risk.

HALP is generally identified incidentally after routine assessment of a lipid profile as it is generally not associated with any signs or symptoms. Generally, patients are asymptomatic and no medical therapy is required.

Cholesterol Ester Transfer Protein (CETP) Deficiency

CETP transfers cholesteryl esters from HDL particles to triglyceride rich lipoproteins and LDL in exchange for triglycerides (9). Individuals who are homozygous for CETP mutations have markedly increased HDL-C levels with normal or modest decreases in LDL-C and apo B levels (33-35). The HDL are large due to the accumulation of cholesterol esters (34). The decrease in LDL-C is due to the failure of cholesterol ester transport from HDL to apo B containing lipoproteins. There is a predominance of small LDL particles. Individuals who are heterozygotes for CETP mutations show modestly elevated HDL-C levels (33). In Japanese individuals with HDL-C levels > 100mg/dL 67% were demonstrated to have CETP gene mutations (36). CETP deficiency is the most important and frequent cause of HALP in Japan. CETP deficiency is common in other Asian populations but is relatively rare in other ethnic groups (34). Despite extensive studies the effect of CETP mutations on the risk of ASCVD is uncertain (33-35).

Endothelial Lipase (EL) Deficiency

Endothelial lipase (EL) is encoded by the LIPG gene and hydrolyzes phospholipids on HDL resulting in smaller HDL particles that are more rapidly metabolized (9). Genetic variants in LIPG have been identified Iin individuals with elevated HDL-C levels (33,34). As one would predict large HDL particles are observed in individuals deficient in EL (34). Whether variants in LIPG leading to decreased EL activity and increased HDL-C levels reduces ASCVD risk is uncertain (33-35). In heterozygotes there are variable effects on HDL-C levels (35).

Hepatic Lipase (HL) Deficiency

Hepatic lipase (HL) is encoded by the LIPC gene and mediates the hydrolysis of triglycerides and phospholipids in intermediate density lipoproteins (IDL) and LDL leading to smaller particles (IDL is converted to LDL; LDL is converted from large LDL to small LDL) (9). It also mediates the hydrolysis of triglycerides and phospholipids in HDL resulting in smaller HDL particles (9). Several case reports of families with elevated HDL-C levels (HALP) caused by a genetically defined HL deficiency have been described (34,35). HL deficiency may also be associated with elevated triglycerides and cholesterol with increased intermediate density lipoproteins (IDL) (35,37). Several HL deficient individuals had premature ASCVD likely due to increased levels of apo B containing lipoproteins (35,37). Heterozygotes do not appear to have discrete lipoprotein abnormalities (37).

Scavenger Receptor Class B Type I (SR-BI)

Scavenger receptor class B type I (SR-BI) is encoded by the SCARB1 gene and facilitates the selective uptake of the cholesterol esters from HDL into the liver, adrenal, ovary, and testes (9). In macrophages and other cells, SR-B1 facilitates the efflux of cholesterol from the cell to HDL particles (9). Mutations in SCARB1 associated with decreased SR-B1 have been observed in individuals with high HDL-C levels (38-40). Heterozygotes have intermediate elevations of HDL-C between wild-type and homozygous individuals. Studies have suggested that some but not all mutations in SCARB1 result in an increased risk of ASCVD despite increased HDL-C levels (35,40). A decrease in adrenal function has been reported in some individuals with SCARB1 mutations likely due to a reduced ability of SR-B1 to facilitate cholesterol uptake into the adrenal glands (39,41). Abnormalities in platelet function have also been observed in some patients (41).

REFERENCES

1. Kjeldsen EW, Thomassen JQ, Frikke-Schmidt R. HDL cholesterol concentrations and risk of atherosclerotic cardiovascular disease - Insights from randomized clinical trials and human genetics. Biochim Biophys Acta Mol Cell Biol Lipids 2021; 1867:159063

2. Feingold KR. Obesity and Dyslipidemia. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Grossman A, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrere B, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Stratakis CA, Trence DL, Wilson DP, eds. Endotext. South Dartmouth (MA) 2020.

3. Schaefer EJ, Anthanont P, Diffenderfer MR, Polisecki E, Asztalos BF. Diagnosis and treatment of high density lipoprotein deficiency. Prog Cardiovasc Dis 2016; 59:97-106

4. Geller AS, Polisecki EY, Diffenderfer MR, Asztalos BF, Karathanasis SK, Hegele RA, Schaefer EJ. Genetic and secondary causes of severe HDL deficiency and cardiovascular disease. J Lipid Res 2018; 59:2421-2435

5. Zanoni P, von Eckardstein A. Inborn errors of apolipoprotein A-I metabolism: implications for disease, research and development. Curr Opin Lipidol 2020; 31:62-70

6. Santos RD, Schaefer EJ, Asztalos BF, Polisecki E, Wang J, Hegele RA, Martinez LR, Miname MH, Rochitte CE, Da Luz PL, Maranhao RC. Characterization of high density lipoprotein particles in familial apolipoprotein A-I deficiency. J Lipid Res 2008; 49:349-357

7. Hooper AJ, Hegele RA, Burnett JR. Tangier disease: update for 2020. Curr Opin Lipidol 2020; 31:80-84

8. Burnett JR, Hooper AJ, McCormick SPA, Hegele RA. Tangier Disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, eds. GeneReviews((R)). Seattle (WA)2019.

9. Feingold KR. Introduction to Lipids and Lipoproteins. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Grossman A, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrere B, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Stratakis CA, Trence DL, Wilson DP, eds. Endotext. South Dartmouth (MA) 2021.

10. Liu M, Chung S, Shelness GS, Parks JS. Hepatic ABCA1 and VLDL triglyceride production. Biochim Biophys Acta 2012; 1821:770-777

11. Bi X, Pashos EE, Cuchel M, Lyssenko NN, Hernandez M, Picataggi A, McParland J, Yang W, Liu Y, Yan R, Yu C, DerOhannessian SL, Phillips MC, Morrisey EE, Duncan SA, Rader DJ. ATP-Binding Cassette Transporter A1 Deficiency in Human Induced Pluripotent Stem Cell-Derived Hepatocytes Abrogates HDL Biogenesis and Enhances Triglyceride Secretion. EBioMedicine 2017; 18:139-145

12. Koseki M, Yamashita S, Ogura M, Ishigaki Y, Ono K, Tsukamoto K, Hori M, Matsuki K, Yokoyama S, Harada-Shiba M. Current Diagnosis and Management of Tangier Disease. J Atheroscler Thromb 2021; 28:802-810

13. Bochem AE, van Wijk DF, Holleboom AG, Duivenvoorden R, Motazacker MM, Dallinga-Thie GM, de Groot E, Kastelein JJ, Nederveen AJ, Hovingh GK, Stroes ES. ABCA1 mutation carriers with low high-density lipoprotein cholesterol are characterized by a larger atherosclerotic burden. Eur Heart J 2013; 34:286-291

14. van Dam MJ, de Groot E, Clee SM, Hovingh GK, Roelants R, Brooks-Wilson A, Zwinderman AH, Smit AJ, Smelt AH, Groen AK, Hayden MR, Kastelein JJ. Association between increased arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux: an observational study. Lancet 2002; 359:37-42

15. Schaefer EJ, Zech LA, Schwartz DE, Brewer HB, Jr. Coronary heart disease prevalence and other clinical features in familial high-density lipoprotein deficiency (Tangier disease). Ann Intern Med 1980; 93:261-266

16. Frikke-Schmidt R, Nordestgaard BG, Stene MC, Sethi AA, Remaley AT, Schnohr P, Grande P, Tybjaerg-Hansen A. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA 2008; 299:2524-2532

17. Frikke-Schmidt R. Genetic variation in the ABCA1 gene, HDL cholesterol, and risk of ischemic heart disease in the general population. Atherosclerosis 2010; 208:305-316

18. Iatan I, Alrasadi K, Ruel I, Alwaili K, Genest J. Effect of ABCA1 mutations on risk for myocardial infarction. Curr Atheroscler Rep 2008; 10:413-426

19. Brunham LR, Singaraja RR, Hayden MR. Variations on a gene: rare and common variants in ABCA1 and their impact on HDL cholesterol levels and atherosclerosis. Annu Rev Nutr 2006; 26:105-129

20. Serfaty-Lacrosniere C, Civeira F, Lanzberg A, Isaia P, Berg J, Janus ED, Smith MP, Jr., Pritchard PH, Frohlich J, Lees RS, et al. Homozygous Tangier disease and cardiovascular disease. Atherosclerosis 1994; 107:85-98

21. Schaefer EJ, Anderson DW, Zech LA, Lindgren FT, Bronzert TB, Rubalcaba EA, Brewer HB, Jr. Metabolism of high density lipoprotein subfractions and constituents in Tangier disease following the infusion of high density lipoproteins. J Lipid Res 1981; 22:217-228

22. Pavanello C, Calabresi L. Genetic, biochemical, and clinical features of LCAT deficiency: update for 2020. Curr Opin Lipidol 2020; 31:232-237

23. Saeedi R, Li M, Frohlich J. A review on lecithin:cholesterol acyltransferase deficiency. Clin Biochem 2015; 48:472-475

24. Pavanello C, Ossoli A, Arca M, D'Erasmo L, Boscutti G, Gesualdo L, Lucchi T, Sampietro T, Veglia F, Calabresi L. Progression of chronic kidney disease in familial LCAT deficiency: a follow-up of the Italian cohort. J Lipid Res 2020; 61:1784-1788

25. Mehta R, Elias-Lopez D, Martagon AJ, Perez-Mendez OA, Sanchez MLO, Segura Y, Tusie MT, Aguilar-Salinas CA. LCAT deficiency: a systematic review with the clinical and genetic description of Mexican kindred. Lipids Health Dis 2021; 20:70

26. Ossoli A, Neufeld EB, Thacker SG, Vaisman B, Pryor M, Freeman LA, Brantner CA, Baranova I, Francone NO, Demosky SJ, Jr., Vitali C, Locatelli M, Abbate M, Zoja C, Franceschini G, Calabresi L, Remaley AT. Lipoprotein X Causes Renal Disease in LCAT Deficiency. PLoS One 2016; 11:e0150083

27. Norum KR, Remaley AT, Miettinen HE, Strom EH, Balbo BEP, Sampaio C, Wiig I, Kuivenhoven JA, Calabresi L, Tesmer JJ, Zhou M, Ng DS, Skeie B, Karathanasis SK, Manthei KA, Retterstol K. Lecithin:cholesterol acyltransferase: symposium on 50 years of biomedical research from its discovery to latest findings. J Lipid Res 2020; 61:1142-1149

28. Freeman LA, Karathanasis SK, Remaley AT. Novel lecithin: cholesterol acyltransferase-based therapeutic approaches. Curr Opin Lipidol 2020; 31:71-79

29. Shamburek RD, Bakker-Arkema R, Auerbach BJ, Krause BR, Homan R, Amar MJ, Freeman LA, Remaley AT. Familial lecithin:cholesterol acyltransferase deficiency: First-in-human treatment with enzyme replacement. J Clin Lipidol 2016; 10:356-367

30. Faguer S, Colombat M, Chauveau D, Bernadet-Monrozies P, Beq A, Delas A, Soler V, Labadens I, Huart A, Benlian P, Schanstra JP. Administration of the High-Density Lipoprotein Mimetic CER-001 for Inherited Lecithin-Cholesterol Acyltransferase Deficiency. Ann Intern Med 2021; 174:1022-1025

31. Motazacker MM, Peter J, Treskes M, Shoulders CC, Kuivenhoven JA, Hovingh GK. Evidence of a polygenic origin of extreme high-density lipoprotein cholesterol levels. Arterioscler Thromb Vasc Biol 2013; 33:1521-1528

32. Dron JS, Wang J, Low-Kam C, Khetarpal SA, Robinson JF, McIntyre AD, Ban MR, Cao H, Rhainds D, Dube MP, Rader DJ, Lettre G, Tardif JC, Hegele RA. Polygenic determinants in extremes of high-density lipoprotein cholesterol. J Lipid Res 2017; 58:2162-2170

33. Larach DB, Cuchel M, Rader DJ. Monogenic causes of elevated HDL cholesterol and implications for development of new therapeutics. Clin Lipidol 2013; 8:635-648

34. Giammanco A, Noto D, Barbagallo CM, Nardi E, Caldarella R, Ciaccio M, Averna MR, Cefalu AB. Hyperalphalipoproteinemia and Beyond: The Role of HDL in Cardiovascular Diseases. Life (Basel) 2021; 11

35. Kardassis D, Thymiakou E, Chroni A. Genetics and regulation of HDL metabolism. Biochim Biophys Acta Mol Cell Biol Lipids 2021; 1867:159060

36. Hirano K, Yamashita S, Kuga Y, Sakai N, Nozaki S, Kihara S, Arai T, Yanagi K, Takami S, Menju M, et al. Atherosclerotic disease in marked hyperalphalipoproteinemia. Combined reduction of cholesteryl ester transfer protein and hepatic triglyceride lipase. Arterioscler Thromb Vasc Biol 1995; 15:1849-1856

37. Weissglas-Volkov D, Pajukanta P. Genetic causes of high and low serum HDL-cholesterol. J Lipid Res 2010; 51:2032-2057

38. Brunham LR, Tietjen I, Bochem AE, Singaraja RR, Franchini PL, Radomski C, Mattice M, Legendre A, Hovingh GK, Kastelein JJ, Hayden MR. Novel mutations in scavenger receptor BI associated with high HDL cholesterol in humans. Clin Genet 2011; 79:575-581

39. Vergeer M, Korporaal SJ, Franssen R, Meurs I, Out R, Hovingh GK, Hoekstra M, Sierts JA, Dallinga-Thie GM, Motazacker MM, Holleboom AG, Van Berkel TJ, Kastelein JJ, Van Eck M, Kuivenhoven JA. Genetic variant of the scavenger receptor BI in humans. N Engl J Med 2011; 364:136-145

40. Zanoni P, Khetarpal SA, Larach DB, Hancock-Cerutti WF, Millar JS, Cuchel M, DerOhannessian S, Kontush A, Surendran P, Saleheen D, Trompet S, Jukema JW, De Craen A, Deloukas P, Sattar N, Ford I, Packard C, Majumder A, Alam DS, Di Angelantonio E, Abecasis G, Chowdhury R, Erdmann J, Nordestgaard BG, Nielsen SF, Tybjaerg-Hansen A, Schmidt RF, Kuulasmaa K, Liu DJ, Perola M, Blankenberg S, Salomaa V, Mannisto S, Amouyel P, Arveiler D, Ferrieres J, Muller-Nurasyid M, Ferrario M, Kee F, Willer CJ, Samani N, Schunkert H, Butterworth AS, Howson JM, Peloso GM, Stitziel NO, Danesh J, Kathiresan S, Rader DJ, Consortium CHDE, Consortium CAE, Global Lipids Genetics C. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. Science 2016; 351:1166-1171

41. Chadwick AC, Sahoo D. Functional genomics of the human high-density lipoprotein receptor scavenger receptor BI: an old dog with new tricks. Curr Opin Endocrinol Diabetes Obes 2013; 20:124-131