Current Status of Familial LCAT Deficiency in Japan

Masayuki Kuroda1, Hideaki Bujo2, Koutaro Yokote3, Takeyoshi Murano4, Takashi Yamaguchi5, Masatsune Ogura6, Katsunori Ikewaki7, Masahiro Koseki8, Yasuo Takeuchi9, Atsuko Nakatsuka10, Mika Hori11, Kota Matsuki12, Takashi Miida13, Shinji Yokoyama14, Jun Wada10 and Mariko Harada-Shiba15

on behalf of the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan†

1Center for Advanced Medicine, Chiba University Hospital, Chiba University, Chiba, Japan
2Department of Clinical-Laboratory and Experimental-Research Medicine, Toho University Sakura Medical Center, Chiba, Japan
3Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan
4Clinical Laboratory Program, Faculty of Science, Toho University, Funabashi, Chiba, Japan
5Center of Diabetes, Endocrinology and Metabolism, Toho University Sakura Medical Center, Chiba, Japan
6Division of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
7Division of Neurology, Anti-Aging, and Vascular Medicine, Department of Internal Medicine, National Defense Medical College, Saitama, Japan
8Division of Cardiovascular Medicine, Department of Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
9Division of Nephrology, Kitasato University School of Medicine, Kanagawa, Japan
10Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
11Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan
12Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
13Department of Clinical Laboratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan
14Institute for Biological Functions, Chubu University, Aichi, Japan
15Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

†The Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan: Mariko Harada-Shiba (Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan), Shun Ishibashi (Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan), Shinji Yokoyama (Institute for Biological Functions, Chubu University, Aichi, Japan), Hitoshi Shimano (Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine University of Tsukuba, Tsukuba, Japan), Koutaro Yokote (Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan), Hideaki Bujo (Department of Clinical-Laboratory and Experimental-Research Medicine, Toho University Sakura Medical Center, Chiba, Japan), Shizuya Yamashita (Rinku General Medical Center, Osaka, Japan), Kazuhisa Tsukamoto (Department of Internal Medicine, Teikyo University, Tokyo, Japan), Toshio Hayashi (School of Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan), Katsunori Ikewaki (Division of Neurology, Anti-Aging, and Vascular Medicine, Department of Internal Medicine, National Defense Medical College, Saitama, Japan), Takanari Gotoda (Department of Metabolic Biochemistry, Faculty of Medicine, Kyorin University, Tokyo, Japan), Kazushige Dobashi (Department of Pediatrics, School of Medicine, University of Yamanashi, Yamanashi, Japan), Yoshihiro Miyamoto (Open Innovation Center, National Cerebral and Cardiovascular Center, Osaka, Japan), Misato Takegami (Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Osaka, Japan), Yosuke Sekijima (Department of Medicine (Neurology & Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan), Masayuki Kuroda (Department of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan), Hiroaki Okazaki (Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan), Atsushi Nohara (Ishikawa Prefectural Central Hospital, Kanazawa, Japan), Shingo Koyama (Division of Neurology and Clinical Neuroscience, Department of Internal Medicine III, Yamagata University Faculty of Medicine, Yamagata, Japan), Kyoko Inagaki (Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Nippon Medical School, Tokyo, Japan), Koh Ono (Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan), Masahiro Koseki (Division of Cardiovascular Medicine, Department of Medicine, Osaka University Graduate School of Medicine, Osaka, Japan), Hiroko Daidai (Faculty of Health Science, Juntendo University, Juntendo University Graduate School of Medicine, Tokyo, Japan), Manabu Takahashi (Division of Endocrinology and Metabolism, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan), Kimitoshi Nakamura (Department of Pediatrics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan), Takashi Miida (Department of Clinical Laboratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan), Masa-aki Kawashiri (Department of Cardiovascular Medicine, Graduate School of Medical Sciences,
around the same time, a patient with deficiency of this enzyme was identified in Norway. A 33-year-old woman in a hospital in Oslo was suspected of having chronic nephritis due to proteinuria and exhibited corneal opacity, anemia, and slight hypoalbuminemia, though renal function was normal. Renal biopsy revealed presence of foam cells in the glomerular tufts. Plasma total cholesterol and triglyceride levels were high but most of the cholesterol was found not to be esterified and further biochemical analyses

**Key words:** Lecithin cholesterol acyltransferase, Low HDL-cholesterol, Abnormal LDL, Corneal opacity, Proteinuria, Enzyme replacement therapy

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**Introduction**

The enzyme that esterifies cholesterol in human plasma was discovered in 1962\(^1\). The reaction was determined to be an acyl transfer reaction from phosphatidylcholine (lecithin) associated with HDL. The enzyme was named LCAT, and the physiological role proposed for it was creating a gradient of cholesterol content between the HDL surface and cell membrane to generate efflux of cell cholesterol\(^2\). At around the same time, a patient with deficiency of this enzyme was identified in Norway. A 33-year-old woman in a hospital in Oslo was suspected of having chronic nephritis due to proteinuria and exhibited corneal opacity, anemia, and slight hypoalbuminemia, though renal function was normal. Renal biopsy revealed presence of foam cells in the glomerular tufts. Plasma total cholesterol and triglyceride levels were high but most of the cholesterol was found not to be esterified and further biochemical analyses

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**Address for correspondence:** Masayuki Kuroda, Center for Advanced Medicine, Chiba University Hospital, Chiba University, 1–8–1 Inohana, Chuou-ku, Chiba 260–8677, Japan. E-mail: kurodam@faculty.chiba-u.jp

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demonstrated that the patient was deficient in LCAT activity. Similar signs and symptoms were also noted in her sister, suggesting a hereditary disorder. Therefore, the disorder was named familial LCAT deficiency (FLD, OMIM 245900) by Norum and Gjone11). The classical form of this disease exhibits plasma LCAT activity of less than 10% of normal whereas, in partial deficiency the decrease may be 15 to 40%. In FLD, there is lack of esterification activity on both HDL and ApoB-containing lipoproteins. Later, a subtype of this disease was found and named fish-eye disease (FED, OMIM 136120), where esterification is inactive only on HDL10). Both FLD and FED are caused by LCAT gene mutations. The profile and progression of the accompanying symptoms vary depending on the extent of LCAT activity impairment. In this review, the clinical and biochemical features, genetic backgrounds and current treatment of this hereditary disease are summarized and, referring to cases reported in Japan, clinical practice guidelines for Japan are proposed.

Background Mechanism for Clinical Findings of Familial LCAT Deficiency and Fish-Eye Disease

LCAT is the enzyme that acyl-esterifies cholesterol in plasma, which reduces unesterified cholesterol on the HDL surface to generate efflux of cell cholesterol to HDL. This comprises an important part of cholesterol transport from peripheral organs and cells to the liver for its catabolism. LCAT dysfunction disrupts this process, resulting in marked reduction of HDL-C and deformation of HDL particles due to lack of their major core lipid, cholesteryl acyl-ester. Impaired turnover of cellular cholesterol leads to its accumulation in cells in the cornea, bone marrow, liver, spleen, and glomerular basement membrane of the kidney4, 5). It is visible from the abnormal shape of erythrocytes4, 5). The clinical prognosis of LCAT deficiency is largely dependent on progression of renal dysfunction4, 5). Both FLD and FED are commonly screened for by low plasma HDL-C level and corneal opacity4, 5). Such as apoA-I with cellular phospholipid and cholesterol (nascent HDL or preβ-HDL), to generate the core and make particles spherical (mature HDL). This process maintains the efflux of cholesterol from cells to HDL. The reaction also takes place on apoB lipoproteins (β-lipoproteins), which should provide additional efflux of cell cholesterol. Lack of LCAT activity therefore causes a marked decrease in HDL-C and “immature” HDL remains in plasma appearing as rouleaux under electron microscopic observation. Owing to this abnormal HDL, plasma apoA-I and apoA-II, the first and second major apolipoproteins, also decrease. Thus, among FLD plasma lipoproteins, the percentage of esterified cholesterol in total cholesterol (CE/TC) is markedly low. There are also abnormal findings for LDL fractions in ultracentrifugation analysis6) due to lack of the LCAT reaction, in which three subtypes of particles with different lipid compositions are evident. They are LpX particles, which are called FC-rich, PL-rich and TG-poor particles, and have a larger size (40 nm-60 nm). A large subtype of LDL rich in TG and PL (Lp8)7) was identified by gel filtration HPLC analysis as a specific subtype for FLD. However, the exact mechanism for generating these abnormal LDL particles is not fully understood. Moreover, specific changes in LDL in FED are not clearly defined.

2) Corneal Opacity

FC and phospholipids accumulate excessively in the cornea due to lack of the LCAT reaction. Corneal turbidity is observed from early childhood in both FLD and FED, with patients presenting severe visual impairment and requiring corneal transplantation. Corneal opacity is frequently observed not only in LCAT deficiency but also in other HDL-deficiencies such as those related to apoA-I and ABCA1 (Tangier disease)8). Electron microscopic studies have shown that corneas from FLD patients are similar to those of patients with familial apoA1 deficiency9, 13). In a patient with Tangier disease, very mild corneal clouding (usually requiring a slit-lamp examination for detection) has been reported, with less abundant extracellular corneal stromal deposits and cholesterol/phospholipid accumulation than in FED14). Since FED is usually not accompanied by renal dysfunction, the underlying mechanisms for corneal opacity and renal dysfunction may differ. Since the largest particle size capable of diffusing through the central stromal matrix is about 12 nm15), it is unlikely that LDL and/or LpX infiltrate into the corneal stroma. On the other hand, small to normal-sized spherical HDL particles are found only in very small amounts in FLD and FED and Tangier disease16-18). As cholesterol is
synthesized in the cornea\(^9\) reduced removal is a possible cause of its accumulation.

3) Hemolytic Anemia

Abnormally shaped erythrocytes, called target red blood cells, appear in LCAT deficiency due to the abnormal lipid composition of the cell membranes, which sometimes leads to hemolytic anemia, perhaps due to their fragility\(^{20, 21}\). The half-life of red blood cells is approximately half that of healthy people.

4) Splenomegaly

Splenomegaly with sea-blue histiocytosis has been reported\(^{22, 25}\) in some FLD patients presenting abnormal lipid profiles. The histiocytes contained cytoplasmic vacuoles and membrane-like structures resembling rose petals, indicating that they were composed of phospholipid-containing membranes.

5) Proteinuria and Renal Dysfunction

Proteinuria is detected relatively early in the life of patients and frequently develops into progressive renal failure at 40 to 50 years of age, and eventually requires hemodialysis\(^{24, 25}\). It has been reported that proteinuria occurred in FLD patients at 3 years of age\(^{26}\). As kidney damage does not generally develop in FED, renal biopsy may be useful for differential diagnosis of the subtypes of LCAT deficiency. Renal lesions begin with deposition of lipid in the glomerular basement membrane, and later in the mesangium and capillary subendothelium. LpX particles, abnormal lipoprotein particles identified in the LDL fractions of FLD, have been considered to be a causative factor of renal damage in many studies\(^5, 27-29\).

Recently, large TG-rich LDL (Lp8)\(^7\) has been reported to be associated with the progression of renal dysfunction. It has also been reported that oxidized lecithin in the LDL of patients causes renal dysfunction\(^30\). In addition, lipoproteins containing apoE have been shown to be taken up by renal glomerular mesangial cells, causing excessive lipid deposition, possibly leading to renal dysfunction\(^31\).

ApoE is a physiological LCAT activator in \(\beta\)-activity on LDL/VLDL particles\(^32\), and effect of \(apoE\) genotype on clinical manifestations has been reported\(^33, 34\), although further analyses are required to draw a definitive conclusion. In mice, LpX is taken up by glomerular endothelial cells, podocytes, and mesangial cells, it causes dysfunction in glomerular endothelial cells, and increases secretion of inflammatory cytokines\(^35\). Recent follow-up studies of families with an FLD mutation for a median of 12 years showed that eGFR deteriorated among homozygous family members at an average annual rate of 3.56 mL/min/1.73 m\(^2\), whereas deterioration in heterozygous members and family controls was 1.33 and 0.68 mL/min/1.73 m\(^2\), respectively\(^36\). A recent Italian cohort study in which 18 FLD patients (12 males and 6 females) were followed up for 12 ± 8.5 years reported that renal events (dialysis, kidney transplant, or death due to renal complications) occur at a median age of 46 years\(^37\).

6) Atherosclerosis

Based on the inverse association between cardiovascular risk and plasma HDL-C levels found in epidemiological studies and the proposed function of LCAT in cholesterol transport, it is conceivable that the risk of cardiovascular events is increased in genetic low HDL-C patients. However, studies on FLD patients have produced inconsistent findings regarding a correlation between LCAT activity and atherosclerosis\(^38, 39\). Recently, Italian and Dutch research groups assessed subclinical atherosclerosis using carotid intima-media thickness in 74 patients with heterozygous mutations leading to the FLD and FED phenotypes\(^40\). Carriers of \(LCAT\) mutations leading to FLD exhibited less carotid atherosclerosis, whereas carriers of those leading to FED showed marginally more atherosclerosis. Thus, the clinical significance of the function of HDL\(^41\) and other LCAT-associated lipoproteins\(^5\) in the progression of atherosclerosis has not been established from the findings in FLD and FED. Also, no significant information in this regard has been reported in Japanese FLD and FED patients.

### Disease Prevalence and Genetics

FLD and FED are autosomal recessive inherited diseases caused by mutations of the \(LCAT\) gene located in the short arm of chromosome 16. In Japan, the prevalence of these diseases is extremely low so the exact rate of mutation is unknown. Fig. 1 shows previously identified \(LCAT\) gene mutations in patients according to The Human Gene Mutation Database\(^42\), showing great diversity in the positions of mutations causing dysfunction of LCAT. An association between position and extent or nature of dysfunction has not been well established. A report by the Ministry of Health, Labor and Welfare Research Group described 13 types of mutations identified in Japan\(^5\) by 2004. Since the report, a further 7 mutations of the \(LCAT\) gene have been identified as causative mutations of FLD or FED in Japan\(^34, 44-46\); 5 of them were novel mutations and 2 had already been reported in patients in other countries. Mutations occurring in Japanese are summarized in Table 1.

| Table 1 |
Fig. 1. Previously identified mutations in LCAT gene

The LCAT gene is composed of six exons. Mutations identified so far are depicted according to The Human Gene Mutation Database (HGMD®) (http://www.hgmd.cf.ac.uk/ac/index.php). Numbers of amino acid residues are expressed based on mature LCAT protein after signal peptide (24 amino acid residues) is cleaved. Mutations in red and blue are causative mutations identified in familial LCAT deficiency (FLD) and fish-eye disease (FED), respectively. The * symbol indicates a mutation reported in Japan, and the # symbol indicates a mutation identified in Japan as well as other countries. Mutations shown in black are variants of uncertain significance found by such as genome-wide nucleotide sequencing of clinical samples.

Table 1. Mutations identified in patients in Japan

| Exon | Mutation | Codon | Amino acid substitution | Phenotype |
|------|----------|-------|-------------------------|-----------|
| 1    | c.86A>T  | 5     | Asn>Ile                 | FLD       |
| 1    | c.101insC| 10    | Pro10fsTer17            | FLD       |
| 1    | c.101C>T | 10    | Pro>Leu                 | FED       |
| 1    | c.110C>T | 13    | Thr>Met                 | FED       |
| 2    | c.160G>A | 30    | Gly>Ser                 | FLD       |
| 2    | c.278C>T | 69    | Pro>Leu                 | FLD       |
| 2    | c.293G>A | 74    | Cys>Tyr                 | FLD       |
| 3    | c.367C>T | 99    | Arg>Cys                 | FED       |
| 4    | c.440C>T | 123   | Thr>Ile                 | FED       |
| 4    | c.490C>T | 140   | Arg>Cys                 | FLD       |
| 4    | c.491G>A | 140   | Arg>His                 | FLD       |
| 4    | c.493insG| 141   | ins Gly                 | FLD       |
| 5    | c.607G>C | 179   | Gly>Arg                 | FLD       |
| 6    | c.756C>A | 228   | Asn>Lys                 | FLD       |
| 6    | c.821C>G | 250   | Pro>Arg                 | FLD       |
| 6    | c.862del | 264   | His263fsTer385          | FLD       |
| 6    | c.950T>C | 293   | Met>Thr                 | FLD       |
| 6    | c.951G>A | 293   | Met>Ile                 | FED       |
| 6    | c.1034C>T| 321   | Thr>Met                 | FLD       |
| 6    | c.1102G>A| 344   | Gly>Ser                 | FLD       |

Mutations identified in Japanese patients are summarized. Note that numbering of amino acid residues is based on mature LCAT protein in which 24 signal peptide sequence is removed.
detection limit in both. Cholesterol esterification rate (CER) \(^{48}\) represents total esterification activity, including \( \alpha \)-activity (specific for \( \alpha \)-lipoproteins) and \( \beta \)-activity. As \( \beta \)-activity is also disrupted in FLD but not much in FED, measured levels are usually more decreased in FLD, compared with FED, which is useful for distinguishing FLD and FED. However, these assays are not routinely available in the clinical laboratories of regular hospitals in Japan. Therefore, the CE/TC ratio in plasma is a useful alternative for distinguishing FLD and FED. CE/TC is always reduced in FLD but not in FED and partial LCAT deficiency. ApoA-I and apoA-II are also significantly reduced due to the reduced HDL levels in FLD and FED. In the electrophoretic analysis of lipoproteins (agarose or polyacrylamide), LCAT dysfunction results in the appearance of abnormal lipoproteins, including LpX and IDL. Large and triglyceride-rich LDL (Lp8) is identified through HPLC gel filtration analysis of lipoproteins\(^7\).

2) Ophthalmic Examination

Corneal opacity (Fig. 3A) is recognized in most LCAT deficiency patients. Grayish white granular spots are observed in corneal layers excluding the epithelium by the slit-lamp test. To assess the extent of corneal opacity, a contrast sensitivity test\(^{49}\) is useful.

Clinical Examinations and Diagnostic Approach to LCAT Deficiency in Japan

The main clinical findings in FLD and FED are corneal opacity and low HDL-C. They are the key signs for suspecting these diseases. Proteinuria and/or anemia are also observed in many cases of FLD, but not in FED.

1) Lipid Examination

HDL-C values reported in the literature are summarized for homozygous and compound heterozygous FLD patients \((n=86)\) in Fig. 2 (until Aug. 2019). More than 72% of patients exhibited HDL-C levels less than 10 mg/dL. However, 3.5% had levels higher than 20 mg/dL though the assay methods were not standardized. When a patient has an HDL-C level less than 25 mg/dL and corneal opacity, LCAT activity analysis should be considered (proposed by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of the Ministry of Health, Labour and Welfare of Japan in 2020). In assays, since \( \alpha \)-activity represents LCAT activity using synthetic HDL (specific for HDL) as a substrate\(^{47}\), measured levels are largely decreased in all plasma samples from patients with FLD or FED and may be below the detection limit in both. Cholesterol esterification rate (CER) \(^{48}\) represents total esterification activity, including \( \beta \)-activity (specific for \( \beta \)-lipoproteins) and \( \alpha \)-activity. As \( \beta \)-activity is also disrupted in FLD but not much in FED, measured levels are usually more decreased in FLD, compared with FED, which is useful for distinguishing FLD and FED. However, these assays are not routinely available in the clinical laboratories of regular hospitals in Japan. Therefore, the CE/TC ratio in plasma is a useful alternative for distinguishing FLD and FED. CE/TC is always reduced in FLD but not in FED and partial LCAT deficiency. ApoA-I and apoA-II are also significantly reduced due to the reduced HDL levels in FLD and FED. In the electrophoretic analysis of lipoproteins (agarose or polyacrylamide), LCAT dysfunction results in the appearance of abnormal lipoproteins, including LpX and IDL. Large and triglyceride-rich LDL (Lp8) is identified through HPLC gel filtration analysis of lipoproteins\(^7\).

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4) Hematological Examination
Mild hemolytic anemia is present in many cases of FLD. A blood count shows a decreased hemoglobin level. HbA1c and haptoglobin levels are also decreased. Red blood cells with an abnormal appearance (called “target cells”, “knizocytes”, “stomatocytes”, or “spherostomatocytes”) are observed in FLD due to cholesterol accumulation in the cell membranes.

5) Gene Analysis
Genetic analysis is useful for the final diagnosis, combined with the results of the above examinations. The recessive inheritance format is determined through identification of mutations in the LCAT gene of the FLD or FED patients.

**Differential Diagnosis**

1) Hereditary Low HDL-Cholesterolemia (Tangier Disease, Familial Hypo-Alpha-Lipoproteinemia and ApoA-I Deficiency)

Patients with apoA-I deficiency and Tangier disease have a marked reduction in plasma HDL-C levels, which are generally lower than those in FLD and FED. Corneal opacity is also observed in these diseases. The apo A-I level is about 30-50 mg/dL in patients with FLD or FED, but levels in Tangier disease are more markedly decreased (less than 10 mg/dL). Thus, the plasma apolipoprotein A-I concentration is useful for the differential diagnosis of these diseases. However, genetic analysis may be needed for final differentiation of diseases with hereditary low HDL-cholesterolemia.

2) Immune-Mediated LCAT Deficiency

There have been reports of patients exhibiting marked reduction in plasma HDL-C and renal dysfunction, similar to those in genetic LCAT deficiency, but are due to the presence of autoantibodies against LCAT protein. Immune-mediated LCAT deficiency is sometimes found through a gradual decrease in HDL-C. Testing for the antibodies and investigation of family history are necessary for differentiating this disorder from genetic LCAT deficiency, especially FLD.

3) Liver Disease (Liver Cirrhosis and Fulminant Hepatitis), Biliary Tract Obstruction, Malnutrition, or Cachexia

LCAT is an enzyme produced in the liver, so its biosynthesis is susceptible to hepatic damage. It is thus necessary to differentiate FLD and FED from
conditions where there is a secondary decrease in the enzyme due to serious liver dysfunction\(^{53}\).

4) Drug-Induced Low HDL-Cholesterolemia (Probucol and Probucol/Fibrates)

Probucol has been found to reduce plasma HDL by inhibiting ABCA1 activity. In addition, it has been reported that plasma HDL is reduced to an extreme degree when probucol is taken with fibrate, even when fibrate is initiated after discontinuing probucol\(^{54-56}\). Patient histories need to be examined for use of these medications.

Since it is a designated intractable disease, diagnostic criteria for familial LCAT deficiency were previously proposed by the research group of the Ministry of Health, Labor and Welfare of Japan. The guidelines have been updated based on additionally accumulated Japanese clinical and laboratory data by a dyslipidemia research group supported by a grant from the Ministry of Health, Labor and Welfare (Table 2).

### Current Treatment

There is no currently approved effective treatment for FLD and FED. Effective treatments would be replacement with normal or recombinant LCAT enzymes and gene therapy, and they are now under development. To mitigate renal dysfunction, a low-fat diet and renoprotective drugs, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), are prescribed.

1) Diet

There has been a study on the FLD siblings where the younger brother, who was put on a low calorie intake (1900 Cal) with fat restriction (25 g/day), did not develop proteinuria while his elder brother having a total calorie intake of 2500 Cal and fat intake of 65 g/day did\(^{57}\). Together with those of other studies\(^{46, 58}\), these findings indicate that development of renal dysfunction can be delayed by a low-fat diet. A low-fat diet may lead to a decrease in abnormal lipoproteins associated with LCAT deficiency as well as reduced renal damage, although it may not be effective in all cases\(^{59}\).

2) Blood Transfusion Therapy

Fresh blood (whole blood or plasma) transfusion therapy has been reported to be effective for LCAT replacement\(^{46, 61}\). An increase in LCAT activity was observed, but it returned to the pre-transfusion level within one week, indicating that it is difficult to maintain a therapeutic level.

3) Drug Treatment

There is no definitive drug treatment for alleviating decreased or defective LCAT activity in FLD. Drug therapy, combined with diet, has been attempted with the purpose of preventing or mitigating the deterioration in renal function. ACE inhibitors reportedly reduced proteinuria after one

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**Table 2. Diagnostic criteria for Japan proposed by research group of Ministry of Health, Labor and Welfare**

| A. Required item | 1. Blood HDL-C level less than 25 mg/dL.  
|                 | 2. Decrease in cholesteryl ester/TC ratio (CE/TC) (60% or less) |
| B. Symptom      | 1. Proteinuria, renal dysfunction  
|                 | 2. Corneal opacities |
| C. Laboratory findings | 1. Anemia (hemoglobin level, less than 11 g/dL)  
|                 | 2. Abnormalities in morphology of red blood cells (called “target cells”, “knizocytes”, “stomatocytes”, or “spherostomatocytes”)  
|                 | 3. Appearance of abnormal lipoproteins (LpX, IDL, or large TG rich LDL) |
| D. Differential diagnosis | 1. Other hereditary low HDL-cholesterolemia (Tangier disease, apolipoprotein A1 deficiency)  
|                 | 2. Secondary LCAT deficiency (pathophysiology showing decreased protein synthesis such as liver disease (hepatic cirrhosis, fulminant hepatitis), biliary obstruction, malnutrition, cachexia, and autoimmune LCAT deficiency with underlying disease)  
|                 | 3. Secondary low HDL-cholesterolemia (After surgery, hepatopathy (especially cirrhosis, severe hepatitis, including convalescent stage), acute phase of systemic inflammatory disease, debilitating diseases such as cancer, history of oral probucol within the past 6 months, probucol and fibrate combination (including prescription after discontinuation of probucol)) |
| E. Genetic testing | 1. Mutation of \( LCAT \) gene |

In a clinical sample in which two essential items are satisfied, the following determinations are made.

**Definite:** A disease that meets one or more of B and C and excludes any disease to be differentiated from in D, and satisfies E

**Probable:** Disease that meets one or more of B and C and excludes any disease that should be differentiated from in D
organ was maintained, but dyslipidemia recurred within 1 year after liver transplantation.

**Future Perspectives**

Our current understanding of familial LCAT deficiency and its complications is summarized in this review based on information from the literature, including that from Japan. More than 100 LCAT mutations have been identified in the world, but mechanisms of development of subsequent complications remain to be elucidated. A better understanding of the pathophysiology of this disease will be necessary to make further progress in treatment. We hope that this review will be helpful for clinicians in performing diagnosis and medical care for patients suspected of having the disease in Japan.

The diagnosis of the subtypes of this rare genetic disease, FLD and FED, requires the involvement of multiple departments such as lipid metabolism, nephrology, and ophthalmology. Also, the onset of severe renal dysfunction is relatively late (40 to 50 years old). These could be reasons for the delay in diagnosis. Measurement of LCAT activity and genetic testing for FLD and FED are not covered by National Health Insurance in Japan, and this also makes it difficult for physicians to diagnose patients with the disease.

Currently, LCAT enzyme replacement therapy by means of transfusion of a recombinant preparation or gene/cell therapy is under development. We hope that these treatments are put into practice in near future, and improve patients' survival and QOL.

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