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Review

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Current Diagnosis and Management of Tangier Disease

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Tangier disease is a genetic disorder characterized by an absence or extremely low level of high-density lipoprotein (HDL)-cholesterol (HDL-C). It is caused by a dysfunctional mutation of the ATP-binding cassette transporter A1 (*ABCA1*) gene, the mandatory gene for generation of HDL particles from cellular cholesterol and phospholipids, and it appears in an autosomal recessive hereditary profile. To date, 35 cases have been reported in Japan and 109 cases outside Japan. With dysfunctional mutations in both alleles (homozygotes or compound heterozygotes), the HDL-C level is mostly less than 5 mg/dL and there is 10 mg/dL or less of apolipoprotein A-I (apoA-I), the major protein component of HDL. In patients with Tangier disease, major physical findings are orange-colored pharyngeal tonsils, hepatosplenomegaly, corneal opacity, lymphadenopathy, and peripheral neuropathy. Although patients tend to have decreased low-density lipoprotein (LDL)-cholesterol (LDL-C) levels, premature coronary artery disease is frequently observed. No specific curative treatment is currently available, so early identification of patients and preventing atherosclerosis development are crucial. Management of risk factors other than low HDL-C is also important, such as LDL-C levels, hypertension and smoking. Additionally, treatment for glucose intolerance might be required because impaired insulin secretion from pancreatic beta cells has occasionally been reported.

Key words: **Tangier disease, HDL, Reverse cholesterol transport, ABCA1, Cholesterol efflux, Orange tonsil, Atherosclerosis**

Introduction

Tangier disease is an autosomal recessive disease characterized by extremely low levels or absence of high-density lipoprotein (HDL)-cholesterol (HDL-C) and apolipoprotein A-I (apoA-I)[1]. The disease was named after Tangier Island in Chesapeake Bay, Virginia, USA, where the first case was discovered in 1960 and reported in 1961[2]. In 1991, generation of HDL particles through the direct action of helical HDL apoproteins on cells was first reported[3], and this was found to be deficient in cells derived from a patient with Tangier disease in 1995[4]. Eventually, ATP binding cassette transporter A1 (*ABCA1*) was identified as the gene responsible for this action and for Tangier disease in 1999[5-7]. Sequential progress in the investigation of HDL biosynthesis showed that HDL particles generated through ABCA1-dependent interaction of apolipoproteins with cells are the main source of plasma HDL. Patients with homozygous or compound heterozygous mutations in the *ABCA1* gene display the phenotype of Tangier disease and heterozygotes have decreases in HDL-cholesterol to various extents.

1. Disease Frequency

The number of cases of Tangier disease reported by 2020 was 35 in Japan and 109 in other countries (possibly including duplicates), indicating that it is a rather rare disease[8, 9]. However, the frequency of dysfunctional mutations in the *ABCA1* gene in the general population is not clear. A recent article using the Exome Aggregation Consortium database reported that 1 in 400 individuals in the general population is a heterozygote for a loss-of-function variant in the *ABCA1* gene on the basis of allele frequencies (frameshift, nonsense and splicing only; not missense), indicating a global prevalence of Tangier disease of at

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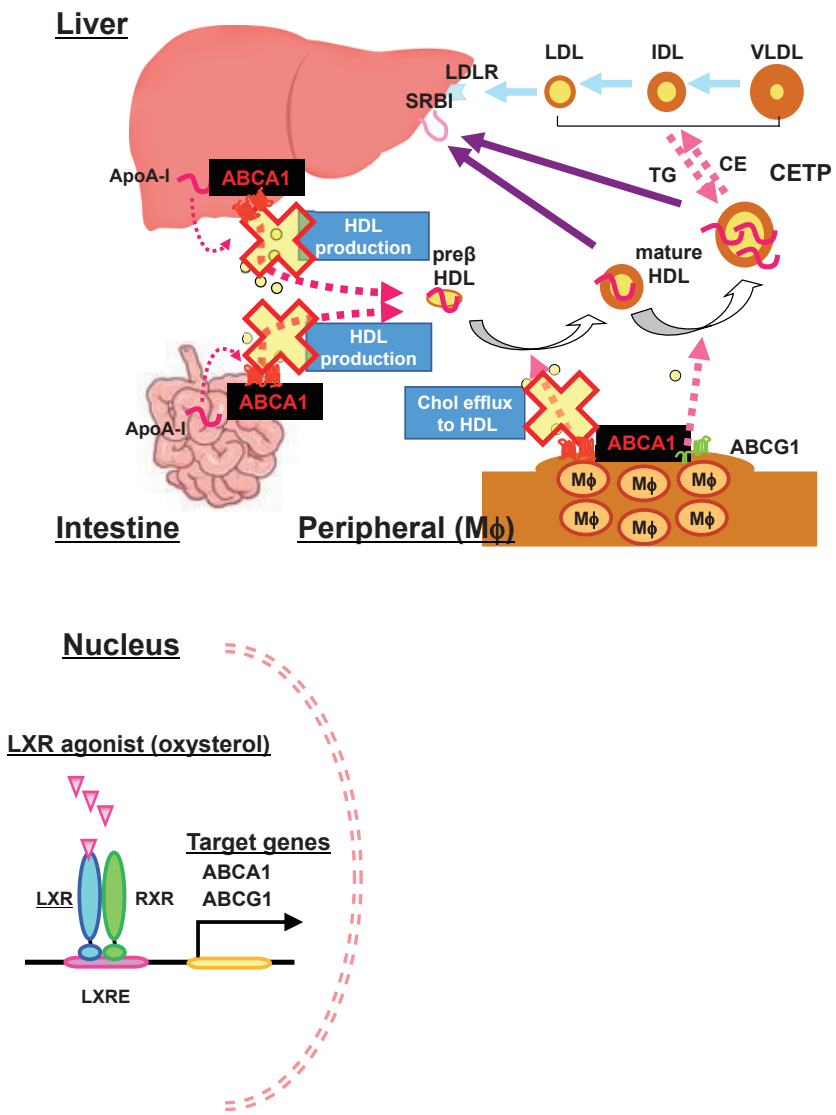

Fig. 1. Roles of ABCA1 in formation of HDL particles, reverse cholesterol transport and pathogenesis of Tangier disease

least 1 in 640,000[10]. It therefore seems that a substantial number of cases might go undiagnosed.

2. Genetic Backgrounds and Pathophysiology

ABCA1 is a member of the ATP-binding cassette transporter membrane protein family. It is an essential factor for generation of nascent HDL particles with extracellular helical apolipoproteins, through transport of cellular phospholipids and cholesterol (Fig. 1). This process is the major source of plasma HDL and one of the major mechanisms of cholesterol export from cells. It may be essential for final processing of cholesterol in mammalian somatic cells that are unable to catabolize cholesterol molecules. Peripheral cells sense intra-cellular cholesterol levels and increase ABCA1 expression for its excretion[11], while it undergoes bidirectional control in hepatocytes to prevent cholesterol recovered from peripheral cells flowing back into blood plasma[12, 13]. With functional deficiency in ABCA1, spherical HDL particles are not produced resulting in extremely low plasma HDL-C levels, which, in Tangier disease patients, are about one third of the normal level. The reason for this is unclear but it has been postulated that a substantial portion of cholesterol molecules in LDL in human plasma are those which have been acyl-esterified in HDL and transferred to VLDL/LDL and that a severe decrease in HDL cholesterol may lead to a decrease in LDL-C level.

In Tangier disease patients, cellular cholesterol export is impaired due to ABCA1 deficiency in peripheral cells, including macrophages and Schwann

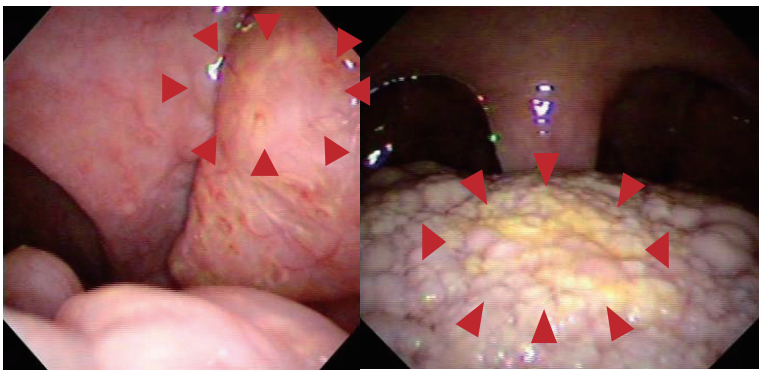

Fig. 2. Orange-colored tonsils observed in male patient with Tangier disease in his 50s
Arrow heads indicate palatine tonsil (left panel) and lingual tonsil (right panel). Reproduced from reference [8].

cells. Cholesterol therefore accumulates in these cells, causing orange-colored pharyngeal tonsillar swelling, corneal opacity, hepatosplenomegaly, lymphadenopathy and peripheral neuropathy. However, impairment of the initial stage of reverse cholesterol transport should be considered to be a risk for developing atherosclerotic diseases even though plasma LDL-C concentrations could be reduced.

ABCA1 appears to destabilize the raft structure, a cholesterol-rich domain of the plasma membrane[14, 15], its deficiency leads to an increase in "lipid" rafts and it has been suggested that this increases secretion of inflammatory cytokines[16]. It has also been reported that the insulinogenic index decreases due to cholesterol accumulation in pancreatic β-cells, which often accompanies glucose intolerance[17, 18]. These metabolic disorders are collectively involved in the development of premature coronary artery disease[8].

In early studies of Tangier disease, Schaefer et al. revealed the kinetics of plasma lipoprotein metabolism using externally labeled injected HDL and found that that apoA-I was catabolized at a much greater fractional rate in patients[19]. Their data, however, should be reinterpreted in terms of external HDL catabolism on the basis of ABCA1 deficiency. A recent study using human pluripotent stem cell-derived hepatocytes has demonstrated that ABCA1 deficiency increases angiopoietin-like protein 3 secretion, which is consistent with increased triglyceride in the plasma of Tangier patients[20].

3. Clinical Manifestations

3.1. Abnormal Plasma Lipoproteins

Plasma HDL-C is mostly low, at 5 mg/dL or less (mean of identified cases 3 ± 3 mg/dL), and the apoA-I concentration is 10 mg/dL or less[21]. Plasma LDL-C is also reduced, to around 37% of the average normal level. The appearance of remnant lipoprotein particles (intermediate products between VLDL and LDL) rich in triglycerides has been reported and this was found to result in abnormal small, dense LDL particles[21]. In subjects with heterozygous mutations of the *ABCA1* gene, plasma HDL-C and apoA-I levels are often reduced to about 50% of that in normal subjects, though the extent of HDL-C decline is not consistent.

3.2. Physical Findings

Impairment of HDL biogenesis results in reduced cholesterol export, which leads to lipid accumulation in cells. A typical finding of this disorder is orange-colored tonsils **(Fig. 2)**[8]. The tonsils of patients are lobulated and swollen and present a bright orange or yellow-grey surface. A history of recurrent tonsillitis or tonsillectomy is often noted. In addition, splenomegaly and associated thrombocytopenia and/or reticulocyte hyperplasia may be present **(Fig. 3)**. Hepatomegaly is also observed in about one-third of cases, but liver dysfunction is not usually present[22]. There is also cholesterol accumulation in other organs, such as lymph nodes, thymus, intestinal mucosa, and skin. Its accumulation in the cornea causes corneal opacity.

3.3. Peripheral Neuropathy

Various peripheral neuropathies, ranging from mild to severe, have been reported. Sensory, motor or mixed disorders appear transiently or persistently. Reduced deep perception and tendon reflexes are rare. Peripheral neuropathy appears as a recurrent asymmetric disorder of peripheral nerves including cranial nerves, as neuropathy with symmetry in the lower limbs, or syringomyelia-like peripheral neuropathy[23, 24].

3.4. Cardiovascular Diseases

It has been reported that 12 out of 35 patients

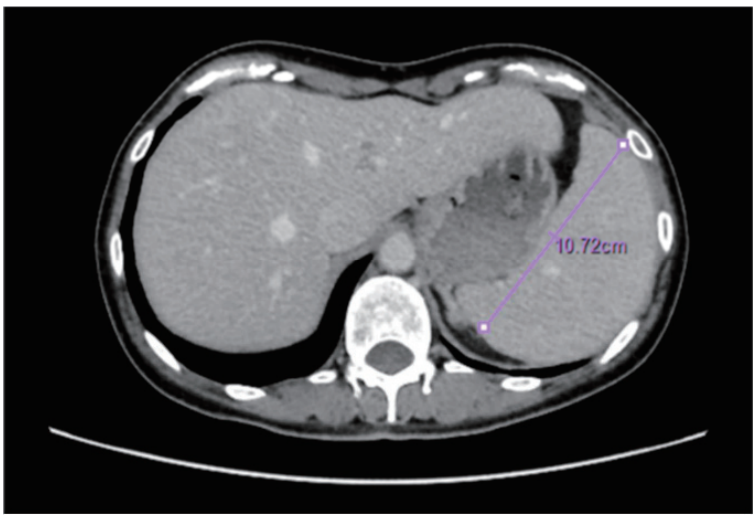

Fig. 3. Abdominal CT scan of splenomegaly in female patient with Tangier disease in her 40s
The photo was kindly provided by one of the co-authors, Prof. Yasushi Ishigaki (Iwate Medical University).

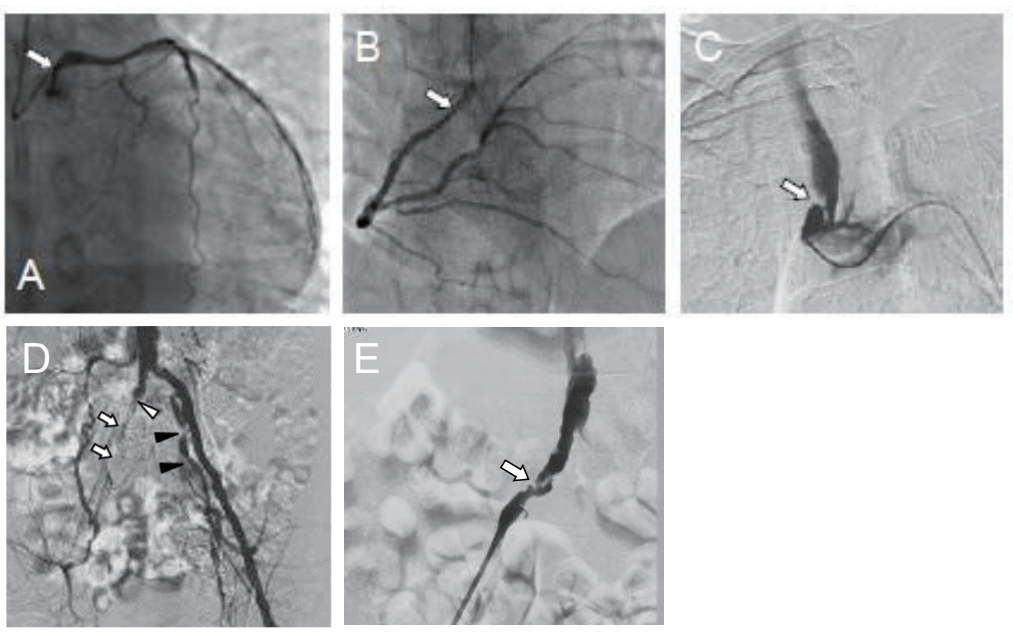

Fig. 4. Advanced systemic atherosclerotic lesions in male patient with Tangier disease in his 50s
Arrows indicate stenosis or occlusion of the artery.
A: left coronary artery, B: right coronary artery, C: brachiocephalic artery, D: left iliac artery, E: right external iliac artery [8].

(34.3%) in Japan and 34 out of 109 patients (31.2%) in other countries had some type of cardiovascular disease, suggesting accelerated atherogenicity in Tangier disease **(Fig. 4)**[8]. A previous case study using intravascular ultrasound (IVUS) revealed diffuse calcified coronary artery lesions[25], which might have been affected by HDL deficiency and glucose intolerance[17].

4. Diagnostic Criteria and Differential Diagnosis

Diagnostic criteria for Tangier disease are given in **Table 1** and the flow chart for differential diagnosis of hypo-HDL-cholesterolemia is shown in **Fig. 5**, based on discussions by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of Japan's Ministry of Health, Labour and Welfare.

Inherited diseases that lead to hypo-HDL-

Table 1. Diagnostic criteria

A. Required laboratory test results
1. Plasma (serum) HDL-cholesterol less than 25 mg/dL
2. Plasma (serum) apoA-I concentration less than 20 mg/dL
B. Clinical symptoms
1. Orange-colored tonsillar swelling
2. Hepatomegaly and/or splenomegaly
3. Corneal opacity
4. Peripheral neuropathy
5. Cardiovascular disease
C. Differential diagnosis
The following diseases should be excluded;
LCAT deficiency, apoA-I deficiency and secondary hypo-HDL-cholesterolemia*
D. Genetic testing**
Identification of pathogenic mutations in the *ABCA1* gene
< Diagnostic category >
Definite: Patients should satisfy both of required laboratory test results (A) AND at least one clinical symptom of (B) AND should be excluded for the diseases of differential diagnosis (C) AND should be positive for genetic testing (D).
Probable: Patients should satisfy both of required laboratory test results (A) AND at least two clinical symptoms of (B) AND should be excluded for the diseases of differential diagnosis (C).
Tangier disease can be diagnosed if patients are categorized "Definite" or "Probable".

*Secondary hypo-HDL-cholesterolemia: After surgery, liver disorders (especially liver cirrhosis and 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, and combined probucol and fibrate (including fibrate administration after discontinuation of probucol).
**When differential diagnosis is difficult, genetic testing for *ABCA1* mutations should be performed. The diagnosis can be definite if pathogenic mutations in the *ABCA1* gene are identified.

cholesterolemia (Familial hypoalphalipoproteinemia) include classical lecithin: cholesterol acyltransferase (LCAT) deficiency, fish-eye disease, and familial apoA-I deficiency. Corneal opacity is commonly observed in these diseases, but tonsillar swelling and peripheral neuropathy are specific to Tangier disease, and xanthomas are found only in familial apoA-I deficiency[24, 26].

Care should be taken to exclude secondary hypo-HDL-cholesterolemia, such as in severe liver diseases, especially liver cirrhosis, and drug-induced hypo-HDL-cholesterolemia, most frequently due to combination of probucol and fibrates. It should be noted that probucol may continue to influence lipid profiles for several months after discontinuation, so HDL-C may be significantly reduced by switching from probucol to fibrates or permafibrate, a selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα), in some cases.

5. Current Management of Tangier Disease

Based on the patients identified in Japan to date, there seem to be no distinct differences in clinical or genetic profiles with patients in other countries[8, 9]. No curative treatment, such as gene therapy for the *ABCA1* gene, has yet been established. Since extremely enhanced risk of atherosclerotic diseases is the major clinical problem, patients should be carefully monitored for presence of atherosclerotic lesions through regular testing including exercise electrocardiography, echocardiography and computed tomography coronary angiography[8]. The management of atherosclerotic risk factors, such as hypertension, smoking and diabetes mellitus, is crucial,[27]. Plasma LDL-C levels are generally low in patients with Tangier disease but if this is not the case, they should be reduced through administration of statins or other means. Impairment of the insulinogenic index should be estimated using a 75 g oral glucose tolerance test[17].

Conclusions and Future Perspectives

Gene therapy for *ABCA1* gene may have the greatest potential for Tangier disease. There is the possibility that restoration of ABCA1 expression in the liver would raise serum HDL-C levels but this might not be enough to recover cellular cholesterol efflux and suppress extra lipid accumulation in cells in atherogenic lesions such as macrophages, smooth muscle cells and endothelial cells. It may not be easy to develop a fundamental therapy for Tangier disease.

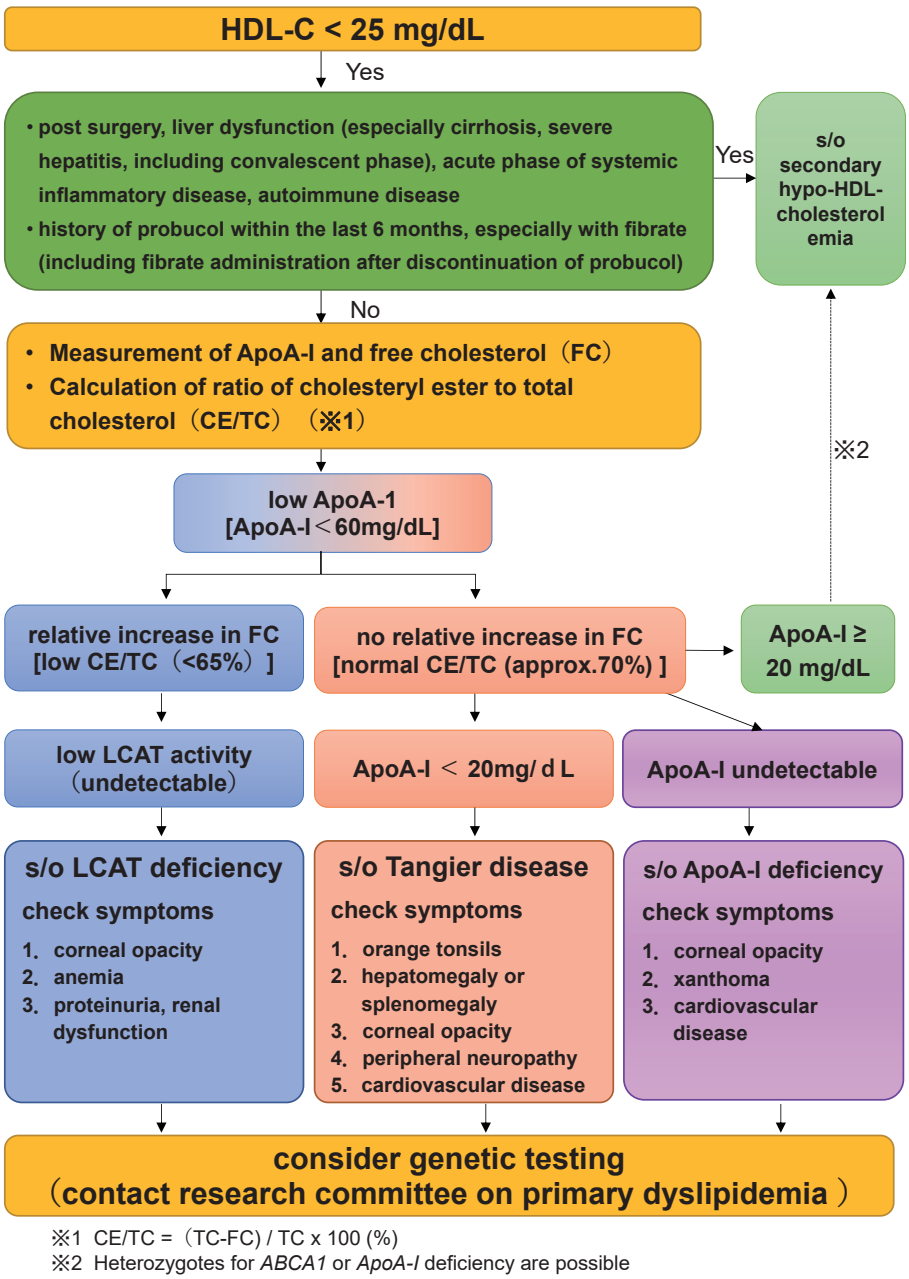

Fig. 5. Differential diagnosis flow chart for hypo-HDL-cholesterolemia

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Conflicts of Interest

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