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# 12

# Tangier Disease

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## 1. Introduction

Various clinical and epidemiological studies have demonstrated an inverse association between high-density lipoprotein (HDL) cholesterol and the risk of coronary events (von Eckardstein et al., 2001). However, it remains controversial whether this relationship is causal or only an epiphenomenon of a more general atherogenic disorder. HDL exerts various potential anti-atherogenic properties. For example, HDL particles transport cholesterol from cells of the arterial wall to the liver and steroidogenic organs, in which cholesterol is used for the synthesis of bile acids, lipoproteins, vitamin D, and steroid hormones (von Eckardstein et al., 2001). In contrast, low HDL cholesterol is frequently identified as a component of metabolic syndrome in many populations, i.e., together with overweight or obesity, glucose intolerance or overt diabetes mellitus, hypertriglyceridemia, and hypertension, which by themselves contribute to the pathogenesis of atherosclerosis (Despres and Marette, 1994). The most severe form of familial HDL deficiency is Tangier disease (TD), which is caused by a genetic disorder.

## 2. HDL metabolism and functions

HDL, isolated by ultracentrifugation, is a lipoprotein with a density in the range 1.063–1.21 g/ml ($HDL_2$, 1.063–1.125 g/ml; $HDL_3$, 1.125–1.21 g/ml) (Havel et al., 1955). However, HDL constitutes a heterogeneous group of particles differing in size, density, lipid composition, apolipoprotein content, and electrophoretic mobility. HDL can be separated into two main subfractions based on electrophoretic mobility, namely the major subfraction has the same mobility as alpha HDL, whereas the other subfractions migrate similar to pre-beta HDL. Most HDL particles in human plasma are alpha HDL, and pre-beta HDL represents only 2–14% of all apolipoprotein A-I (apoA-I) (Ishida et al., 1987; Kunitake et al., 1985).
HDL has a very complex metabolism associated with several HDL-related genes and is synthesized via a complex pathway. Although the underlying genetic defects in many cases of primary low HDL cholesterolemia are not clearly understood, mutations in three pivotal genes, namely apoA-I, lecithin:cholesterol acyltransferase, and ATP-binding cassette transporter A1 (ABCA1) are associated with low plasma HDL cholesterol levels (Miller et al., 2003). Some mutations of these genes are also associated with an increased risk of premature coronary artery disease (CAD).

## 3. Characters of TD

### 3.1 Clinical manifestations of TD

The most severe form of HDL deficiency is TD, first described by Fredrickson et al. (Fredrickson et al., 1961). The plasma lipid profiles in a typical TD patient (TD case 1) with peripheral neuropathy (Uehara et al., 2008a) and those of her younger brother are shown in Table 1. The biological hallmark of plasma in patients with TD is a deficiency of HDL cholesterol, low levels of low-density lipoprotein (LDL) cholesterol, and moderate hypertriglyceridemia. The concentration of apoA-I in plasma of patients with TD is 3% less than that in healthy subjects. TD is a rare autosomal recessive disorder characterized by the absence or extremely low levels of HDL cholesterol and apoA-I in plasma. Furthermore, cholesteryl esters accumulate in many macrophage-rich tissues including the tonsils, liver, spleen, peripheral nerves, lymph nodes, thymus, and arterial walls. Clinical symptoms in homozygotes include hyperplastic orange-yellow tonsils (Fig. 1), hepatosplenomegaly, corneal opacification, and premature CAD in 50% of cases, as well as relapsing peripheral neuropathy due to cholesteryl ester deposition in macrophages and Schwann cells (Assman et al., 1995; Fredrickson et al., 1961; Hobbs and Rader, 1999).

| | | Standard value | Tangier disease (Case) | Younger brother of case |
|---|---|---|---|---|
| Age, gender | | | 50, Female | 48, Male |
| Mutation with ABCA1 gene | | | homozygote, T940M | homozygote, T940M |
| Total Cholesterol | (mg/dl) | 150-219 | 66 | 61 |
| Triglyceride | (mg/dl) | 50-149 | 204 | 191 |
| HDL Choletserol | (mg/dl) | 40-86 | < 5 | < 5 |
| LDL Cholesterol | (mg/dl) | 70-139 | 27 | 33 |
| Apolipoprotein A-I | (mg/dl) | 119-155 | < 5 | < 5 |
| Apolipoprotein A-II | (mg/dl) | 25.9-35.7 | 1.9 | 2 |
| Apolipoprotein B | (mg/dl) | 73-109 | 93 | 76 |
| Apolipoprotein C-II | (mg/dl) | 1.8-4.6 | 4.3 | 0.5 |
| Apolipoprotein C-III | (mg/dl) | 5.8-10.0 | 5.9 | 3.5 |
| Apolipoprotein E | (mg/dl) | 2.7-4.3 | 3.9 | 2.9 |
| RLP cholesterol | (mg/dl) | < 7.5 | 3.4 | 5.5 |
| Phospholipids | (mg/dl) | 160-260 | 85 | 90 |
| Total Bile Acids | (μmol/L) | < 10.0 | 38.8 | 22.0 |

Table 1. Serum lipid profiles in patient with Tangier disease

### 3.2 ABCA1 and TD

In 1999, TD was determined to be caused by a defect in the ABCA1 gene (formerly known as ABC1) (Brooks-Wilson et al., 1999; Rust et al., 1999; von Eckardstein et al., 2001) that is located on chromosome 9q31 and is composed of 50 exons spanning a region of approximately 149 kb (Remaley et al., 1999; Santamarina-Fojo et al., 2000). ABCA1 has been identified as a pivotal gene in the regulation of plasma levels of HDL cholesterol and cellular cholesterol homeostasis, which is defective in patients with TD. In these patients and their heterozygous relatives, ABCA1 gene mutations cause gene dose-dependent decreases in plasma levels of HDL cholesterol and in the capacity of skin fibroblasts and monocyte-derived macrophages to release cholesterol in the extracellular presence of apolipoproteins (Bodzioch et al., 1999; Brooks-Wilson et al., 1999; Lawn et al., 1999; Rust et al., 1999; von Eckardstein et al., 2001).

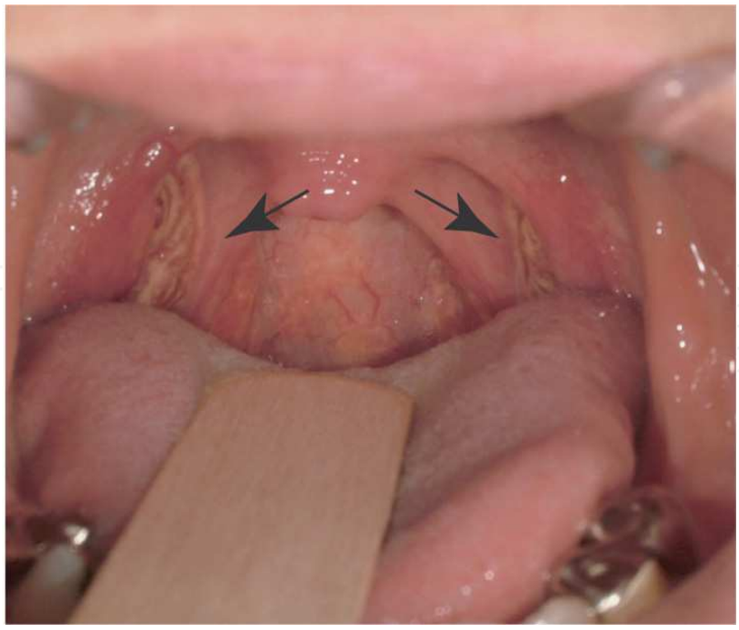


Fig. 1. Photograph of the oral cavity in a patient with Tangier disease reveals swollen orange colored tonsils with yellow lines (arrows). In a genetic sequence analysis, a homozygous missense point mutation was identified at nucleotide 2819 (mRNA position, AB055982) with a C to T mutation in exon 19. Thr940 was substituted by Met940 on the ATP-binding cassette transporter A1 (ABCA1) protein, which was found in the Walker-A motif, as the first nucleotide binding fold of the ABCA1 gene

ABC transporters are transmembrane proteins that facilitate the transport of specific substrates across the membrane in an ATP-dependent manner. ABCA1 is a member of the ABC transporter superfamily, which comprises 48 human transporters; the superfamily is divided into seven subfamilies, including full- or half-transporters, designated ABC A–G. ABC transporters are integral membrane proteins that transport various substrates such as lipids, peptides, amino acids, carbohydrates, vitamins, ions, glucuronides, glutathione conjugates, and xenobiotics to different cellular compartments (Dean and Annilo, 2005; Klein et al., 1999). ABC transporters are defined by the presence of nucleotide binding domains (NBD) that interact with ATP. These domains have two conserved peptide motifs, known as Walker-A and Walker-B, which are present in many proteins that utilize ATP (Walker et al., 1982). The ABC transporters also have a unique amino acid signature between the two Walker motifs that define ABC superfamilies (Klein et al., 1999).

Human ABCA1 belongs to the ABCA subfamily, which is composed of 12 full-transporters denoted ABCA1–13 (with the absence of a functional ABCA11) (Dean et al., 2001). All ABCA transporters are full-size transporters with 1543–5058 amino acids. Structurally, ABCA1 is a 2261 amino acid membrane transporter that is integrated into the membrane via transmembrane domains composed of six transmembrane helices. In addition, ABCA1 has two transmembrane domains and two nucleotide binding domains and is predicted to have an N-terminus oriented to the cytosol with two large extracellular loops (Fig. 2). ABCA1 is expressed in several human organs, with the highest expression levels occurring in the placenta, liver, lung, adrenal glands, and fetal tissues (Langmann et al., 1999).

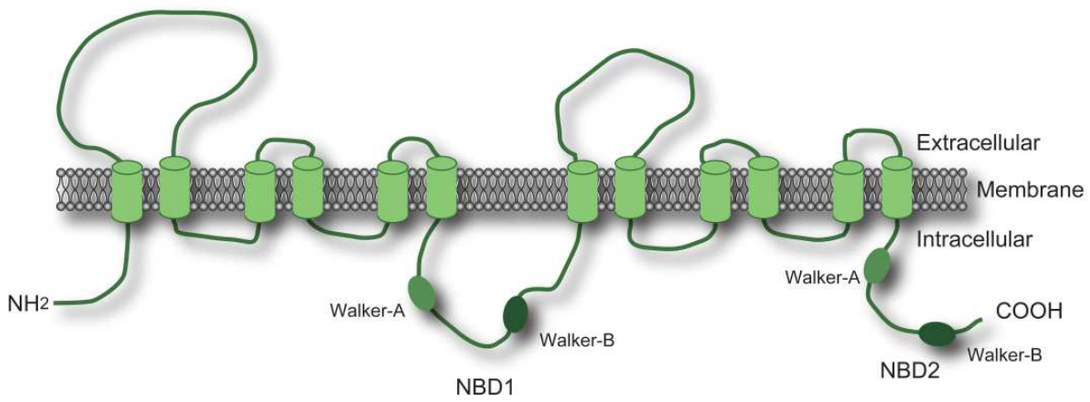



Fig. 2. Structure of the ATP-binding cassette transporter A1 (ABCA1) transporter. The ABCA1 protein consists of 2201 amino acids with two transmembrane domains composed of six transmembrane helices and two nucleotide binding domains (NBD-1 and NBD-2) containing two conserved peptide motifs known as Walker-A and Walker-B. It is predicted to have an N-terminus oriented into the cytosol and two large extracellular loops

## 4. Roles of ABC transporters in HDL metabolism

### 4.1 Functions of ABCA1 and its relationship to HDL metabolism

ABCA1 proteins transport cholesterol or phospholipids (PLs) from the membranous inner leaflet to the outer leaflet, and lipid-free or lipid-poor apoA-I subsequently takes up the transported cholesterol and PLs to form nascent HDL (Oram and Lawn, 2001). ABCA1 localizes to the plasma membrane and intracellular compartments, where it could potentially facilitate transport of lipids to either cell surface-bound (Neufeld et al., 2001) or internalized apolipoproteins (von Eckardstein and Rohrer, 2009). HDL metabolism has at least three steps. First, lipid-free or lipid-poor apoA-I removes free cholesterol from peripheral cells via ABCA1 to form nascent HDL. Second, nascent HDL is lipidated to mature HDL. Third, mature HDL interacts with other apoB containing triglyceride-rich lipoproteins (TRLs) such as very low density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). Therefore, ABCA1 is necessary to form nascent HDL and is an important key molecule in the initial step of the reverse cholesterol transport (RCT) pathway. Cultivated monocyte-derived macrophages from a normolipidemic healthy subject showed an approximately 125% increase in cholesterol efflux of lipid-free apoA-I, whereas macrophages derived from patients with TD did not respond to apoA-I during cholesterol efflux (Fig. 3A). Although cultivated monocyte-derived macrophages showed an increase in cholesterol efflux by lipid-free apoA-I in healthy subjects, the macrophages from patients with TD did not change apoA-I-mediated cholesterol efflux. These results demonstrate that apoA-I-mediated cholesterol efflux depends on ABCA1 in macrophages. Furthermore, ABCA1 plays a pivotal role in mediating PL and cholesterol efflux by lipid-free apoA-I, and thereby, in the formation of discoidal HDL precursors. However, ABCA1 interacts poorly with $HDL_2$ and $HDL_3$. Due to a genetic defect in ABCA1, patients with TD have an extremely low level of HDL and cannot form nascent HDL particles.

Disruption of the ABCA1 gene in mice results in an HDL deficiency and impaired cholesterol transport (McNeish et al., 2000; Orso et al., 2000), and overexpression of ABCA1

leads to increased apoA-I-mediated cholesterol efflux in transgenic mice (Singaraja et al., 2001; Vaisman et al., 2001). These results indicate that ABCA1 is a pivotal gene in the regulation of plasma HDL cholesterol and cellular cholesterol homeostasis.

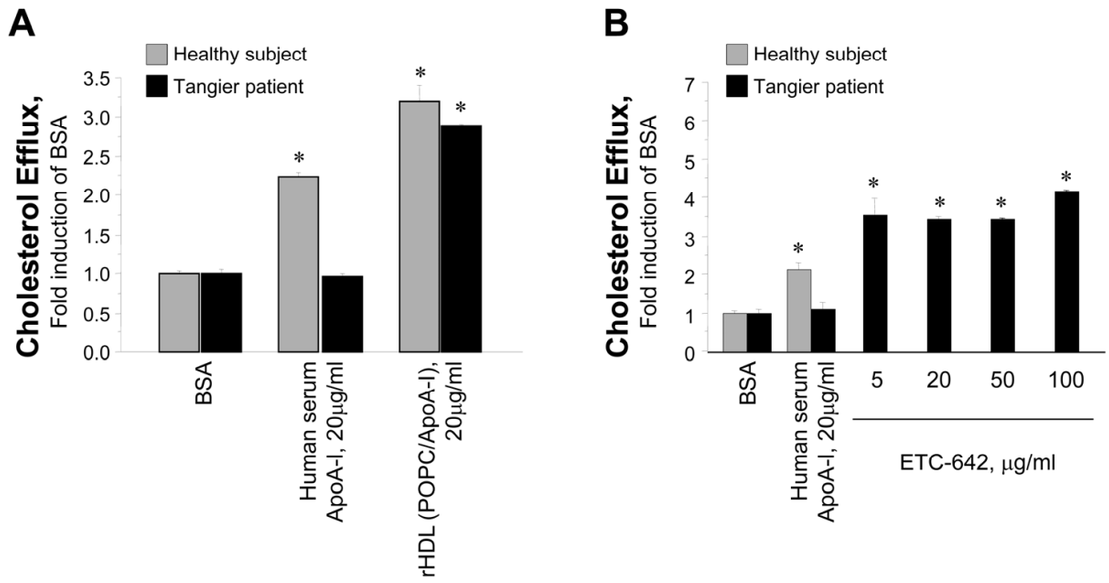



Fig. 3. Cellular cholesterol efflux from monocyte-derived macrophages in the peripheral blood of a patient with Tangier disease (TD). The human monocyte-derived macrophages from a healthy subject and a patient with TD were radiolabeled with $^{3}$H-cholesterol. The cells were then equilibrated with 30 μg/ml cholesterol. Cholesterol efflux was induced by 4-h incubation with 20 μg/ml apolipoprotein A-I (apoA-I) and rHDL (POPC/apoA-I disc) (A) or ETC-642 (phospholipid (PL)/apoA-I mimetics) (B) using a previously modified method (Uehara et al.: *Diabetes* 2002;51:2922–8, Uehara et al.: *Atherosclerosis* 2008;197(1):283–9). rHDL, reconstituted HDL (POPC/apoA-I disc); ETC-642, synthetic peptide of 22 amino acids with 1,2-dipalmitoyl-sn-glycero-3-phosphocholine. n = 3–7; *P < 0.001 vs. BSA

### 4.2 Mechanisms of ABCA1 gene regulation

Cellular cholesterol efflux and ABCA1 expression are upregulated by cholesterol (Langmann et al., 1999; Lawn et al., 1999), oxysterols (Costet et al., 2000), rexinoids (Repa et al., 2000), and cAMP analogs (Bortnick et al., 2000; Lawn et al., 1999). The ABCA1 gene promoter has been analyzed (Costet et al., 2000; Santamarina-Fojo et al., 2000). Ligands of the nuclear transcription factor liver-X-receptors (LXRα and LXRβ) and retinoid-X-receptor alpha (RXRα), i.e., oxysterols and retinoids, respectively, have been identified as enhancers of ABCA1 gene expression (Costet et al., 2000; Oram et al., 2000; Repa et al., 2000; Venkateswaran et al., 2000). LXR and RXR form obligate heterodimers that preferentially bind to response elements within the ABCA1 gene promoter (Santamarina-Fojo et al., 2000; Wang et al., 2001). LXRα/β and RXRα bind to the response element direct repeat 4 (DR4)—two direct hexameric repeats separated by four nucleotides on the ABCA1 promoter that are activated by oxysterols and retinoic acid (Bungert et al., 2001; Willy et al., 1995). Binding of either one or both ligands activates ABCA1 transcription. Treating cells with either an oxysterol or 9-*cis*-retinoic acid induces ABCA1 expression, and their combined treatment

has a marked synergistic effect (Schwartz et al., 2000). The activator of peroxisome proliferator activating receptor (PPAR)-α or -γ also enhances ABCA1 transcription in cultivated cells, but this stimulated ABCA1 transcription depends on an indirect effect by PPARs via upregulation of LXR expression. By contrast, the zinc finger protein ZNF202 transcription factor is a major repressor of ABCA1 transcription. Besides these regulatory factors, unsaturated fatty acids, but not saturated fatty acids, markedly inhibit ABCA1-mediated cholesterol efflux from macrophages because they act as antagonists during oxysterol binding to LXR (Uehara et al., 2002; Uehara et al., 2007). In addition to ZNF202 and unsaturated fatty acids, several potent transcription factors such as USF1, USF2, Fra2, and Sp3 are repressors of ABCA1 transcription (Yang et al., 2002).

### 4.3 Other ABC cholesterol transport proteins

ABCG1 (formerly known as ABC8), another member of the ABC transporter superfamily, has been mapped to chromosome 21q22.3 (Chen et al., 1996; Croop et al., 1997; Dean et al., 2001; Klucken et al., 2000; Savary et al., 1996; Walker et al., 1982). In contrast to ABCA1, ABCG1 is a half-transporter containing only one NBD and a transmembrane domain (Dean et al., 2001; Walker et al., 1982). Therefore, it is thought that ABCG1 requires a dimeric partner to become active. Wang et al. recently reported that ABCG1 and ABCG4 contribute to $HDL_2$- and $HDL_3$-dependent cellular cholesterol efflux (Wang et al., 2004) and appear to have an important function related to HDL lipidation (Smith, 2006; Uehara et al., 2008b; Wang et al., 2004).

Administering a high-fat high-cholesterol diet to ABCG1-deficient mice results in massive accumulation of lipids in tissue macrophages, whereas overexpression of human ABCG1 protects murine tissues from dietary fat-induced lipid accumulation (Kennedy et al., 2005). Furthermore, Mauldin et al. have shown that reduced ABCG1 function facilitates foam cell formation in type 2 diabetic mice (Mauldin et al., 2006). Transplantation of ABCG1-deficient ($ABCG1^{-/-}$) bone marrow into LDL receptor-deficient mice produces contrasting effects on atherosclerotic formation (Baldan et al., 2006; Out et al., 2006; Ranalletta et al., 2006). In contrast, a decrease in lesion formation and size has been observed in the absence of macrophage ABCG1 in mice (Baldan et al., 2006; Ranalletta et al., 2006). Total body expression of ABCG1 protects against the development of early atherosclerotic lesions (Out et al., 2007). However, the physiological roles of ABCG1 and its contribution to the progression of atherosclerosis in humans remain unclear. In addition to the nonspecific and passive pathway, mature-HDL particles, which are spherical and transport almost all HDL cholesterol, appear to induce cholesterol efflux via other ABC transporters, such as ABCG1 and ABCG4, rather than ABCA1 (Uehara et al., 2008b; Wang et al., 2004).

## 5. Lipoprotein profiles in TD measured by capillary isotachophoresis (cITP)

cITP is a newly established technique for characterizing plasma lipoprotein subfractions according to their electric charges. We have previously shown that plasma lipoproteins can be separated into eight fractions consisting of three HDL fractions with fast (fHDL), intermediate (iHDL), and slow (sHDL) electromobility, a fast VLDL fraction (fVLDL), a slow VLDL/IDL fraction (sVLDL),two LDL fractions with fast (fLDL) and slow (sLDL) electromobility, and a minor LDL fraction (mLDL) (Zhang et al., 2005) in normolipidemic (NL) subjects. Figure 4 shows the plasma lipoprotein profiles as characterized by cITP analysis in healthy NL subjects (Fig. 4A) and in two patients with TD (Fig. 4B and C). The

plasma lipoprotein profiles have a characteristic lipoprotein pattern in patients with TD, namely their fasting plasma shows an extremely low signal in the three HDL fractions (peaks 1, 2, and 3) (Fig. 4B-a, B-d, C-a, and C-d). Moreover, while the sLDL fraction corresponding to native LDL (peak 7) was extremely reduced, the sVLDL and fLDL fractions corresponding to electronegative LDL (some oxidized LDL, βVLDL, small dense LDL, or modified LDL) were significantly enhanced. Interestingly, peaks 4 and 5, TRLs, were identified in the LDL subfraction of plasma from patients with TD, which is usually detected only in the VLDL/IDL subfraction but not in LDL in NL plasma. These findings indicate that patients with TD not only have a deficiency in HDL particles but also have a characteristic lipid composition for other lipoproteins such as triglyceride-rich LDL.

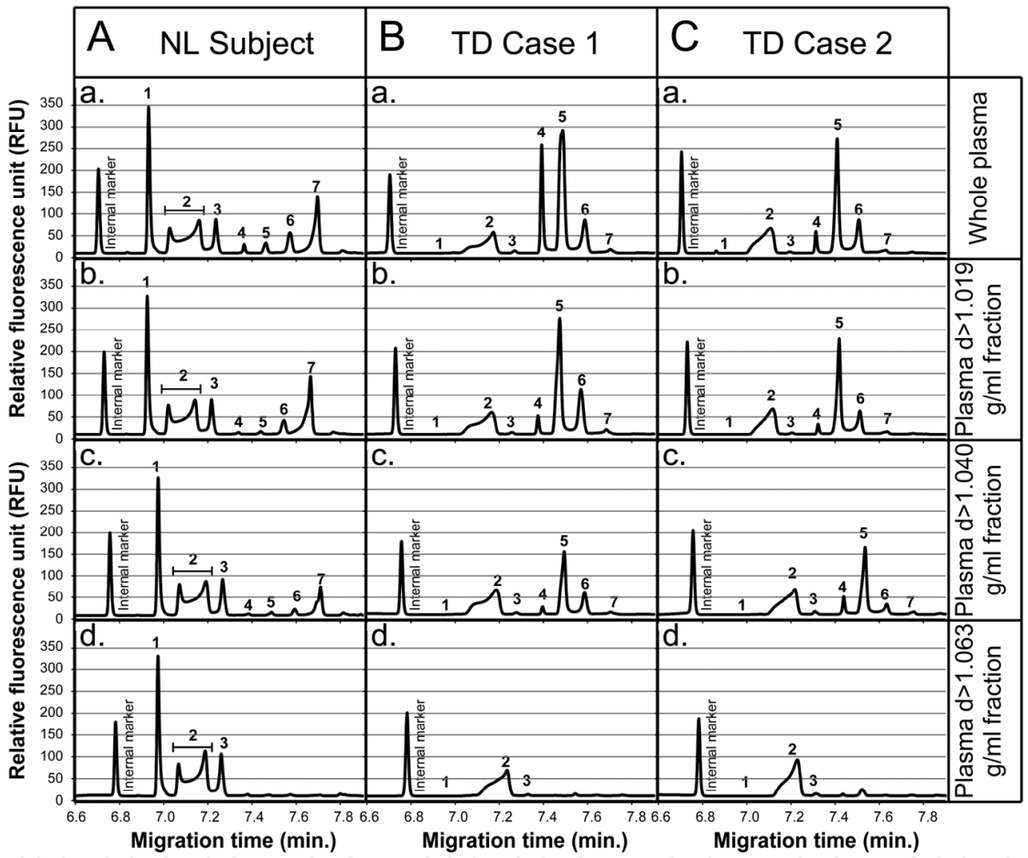



Fig. 4. Lipoprotein subfractions in whole plasma (a) and plasma density (d) > 1.019 g/ml (b), d > 1.040 g/ml (c), and d > 1.063 g/ml (d) fractions by ultracentrifugation in a normolipidemic (NL) subject (A) and two patients with Tangier disease (TD): Case 1, Thr940Met (B) and Case 2, Lys913X (C), as analyzed by capillary isotachophoresis. HDL peaks were not detected in whole plasma (a) or the HDL fraction (d) in patients with TD. Interestingly, peaks 4 and 5, triglyceride-rich lipoproteins (TRLs), were identified in the LDL subfraction of plasma from patients with TD, which was only detected in the VLDL/IDL subfraction but not in LDL in NL plasma. Peaks 1–3: fast-, intermediate-, and slow-migrating HDL; peaks 4 and 5 in a: fast- (fTRL) and slow-migrating (sTRL), respectively; peaks 4 and 5 in b, c: very-very-fast- and very-fast-migrating LDL (vvfLDL and vfLDL), respectively; peaks 6 and 7: fast- and slow-migrating LDL (fLDL and sLDL), respectively

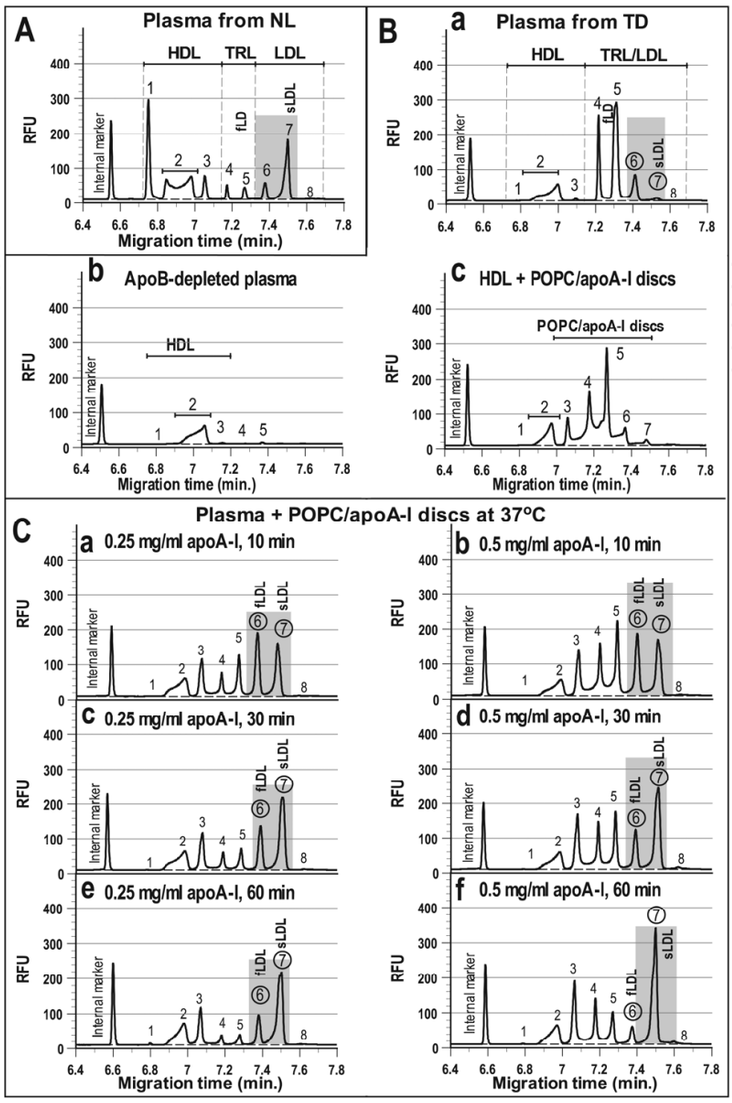



Fig. 5. Effects of 1-palmitoyl-2-oleoylphosphatidylcholine (POPC)/apolipoprotein A-I (apoA-I) discs on lipoprotein profiles in plasma from normolipidemic (NL) subjects (A) and a patient with Tangier disease (TD) (B) as characterized by capillary isotachophoresis (cITP). cITP lipoprotein profiles in apoB-depleted plasma from a patient with TD (B-b). Direct effects of discoidal reconstituted-HDL (rHDL) and the POPC/apoA-I disc (500 μg/ml) on the cITP lipoprotein profile in apoB-depleted plasma from a patient with TD (B-c). Time-dependent effects of rHDL and the POPC/apoA-I disc on the lipoprotein profiles by cITP (C). Lipoprotein profiles in plasma from a patient with TD in the presence (C-a–C-f) of POPC/apoA-I discs as characterized by cITP. Two doses (250 and 500 μg/ml) of POPC/apoA-I discs were incubated *in vitro* with whole plasma at 37ºC from a patient with TD. The POPC/apoA-I discs were incubated with plasma for 10 min (C-a and C-b), 30 min (C-c and C-d), or 60 min (C-e and C-f), respectively.
Peaks 1–3, fast (fHDL), intermediate (iHDL), and slow (sHDL) fractions; peaks 4, 5, fast VLDL (fVLDL) and VLDL/IDL (sVLDL) fractions; peaks 6–8, fast (fLDL), slow (sLDL), and minor LDL (mLDL) fractions. TRL, triglyceride-rich lipoprotein

## 6. Therapeutic approach for HDL deficiency and TD

Although the inhibition of cholesteryl ester transfer protein, PL transfer protein, or scavenger receptor BI and activation of apoA-I or ABCA1 increase HDL cholesterol, the effects of such interventions on atherosclerosis are uncertain in light of studies on animal models and inborn errors of human HDL metabolism. However, no small molecule has been found that strongly stimulates apoA-I production. An LXR agonist is a candidate for increasing HDL cholesterol by increasing ABCA1 expression and HDL cholesterol levels, and RCT also induces hypertriglycemia as a result of the induction of hepatic VLDL production. Substituting or mimicking apoA-I and other potentially anti-atherogenic HDL components has been attempted. Intravenous infusion of an apoA-I variant called apoA-I Milano rapidly decreases atherosclerotic plaque volumes (Nissen et al., 2003). Because TD is a rare genetic disorder, the basic treatment for the disease is still unknown. The development of neuropathy or atherosclerosis in patients with TD is based on a disorder of cellular cholesterol excretion as the initial step of RCT. If the process is able to performed in vitro, it leads to the generation of HDL particle, which can take up the excessive cholesterol from peripheral cell, and it acts as a new therapeutic target without using gene therapy in patients with TD. Reconstituted HDL (rHDL), which is a complex of apoA-I or apoA-I mimetics with PL, must be disc shaped and may be a candidate medication for patients with TD. ApoA-I-mediated cholesterol efflux depends on ABCA1 in macrophages, and ABCA1 plays a pivotal role in mediating PL and cholesterol efflux to lipid-free apoA-I, and thereby, in the formation of discoidal HDL precursors. Mature HDL particles, which are spherical and transport almost all HDL cholesterol, appear to induce cholesterol efflux via other ABC transporters, such as ABCG1 and ABCG4, rather than ABCA1 (Wang et al., 2004). Therefore, we prepared a discoidal reconstituted HDL, which is a complex with apoA-I that contains 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) (Rye et al., 1997). Interestingly, the apoA-I complex with POPC/apoA-I discs was able to take up cholesterol from macrophages in patients with TD and normal subjects (Fig. 3A). Moreover, ETC-642, a newly developed PL/apoA-I mimetic, is a synthetic peptide of 22 amino acids that contains 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine and also works on cholesterol efflux in macrophages of patients with TD as well as the POPC/apoA-I disc (Fig. 3B).

rHDL and the POPC/apoA-I discs not only have a beneficial action on cholesterol efflux in macrophages but are also involved in lipoprotein–lipoprotein interactions in circulating plasma. To clarify the direct effects of the POPC/apoA-I discs in plasma from patients with TD, 250 and 500 μg/ml discs (final concentrations) were incubated with plasma at 37°C (Fig. 5C). After incubation, peaks 4 and 5 comprised TRLs, such as VLDL, and time dependently decreased in addition to an increase in peak 3 as sHDL. The POPC/apoA-I discs did not affect the native-LDL subfraction; however, surprisingly, the native-LDL subfraction was time dependently generated in plasma from patients with TD by incubating it with POPC/apoA-I discs at 37°C. von Eckardstein et al. have shown that lipid-poor HDL precursors are converted into mature, lipid-rich HDL by acquiring PLs and unesterified cholesterol from either cells or apoB-containing lipoproteins or through association with additional lipoprotein (von Eckardstein et al., 1998b). In contrast to normal subjects, the plasma of patients with TD does not convert preβ-HDL into α-HDL, which is believed to be related to the absence of a lipid transfer factor in the cells and plasma of patients with TD (Huang et al., 1995; von Eckardstein et al., 1998a). Thus, a deficiency in HDL composition leads to suppression of the interaction with lipoproteins, which may result in an increase in

TRLs and a decrease in native-LDL with cholesterol conversion among lipoproteins. Shahrokh et al. have shown that PL uptake by LDL contributes to form larger LDL particles (Shahrokh and Nichols, 1985), suggesting that the POPC/apoA-I discs might produce a large-sized LDL particle from a small-sized LDL particle using cholesterol-poor LDL in patients with TD. Although the plasma total concentrations of cholesterol and triglycerides do not change following incubation with POPC/apoA-I discs *in vitro*, the discs may transfer the cholesterol or triglycerides, resulting in changes in the lipoprotein components. These results suggest that the formation of mature-HDL particles by adding POPC/apoA-I discs led to physiological lipoprotein patterns such as higher native-LDL and lower TRLs in circulating plasma.

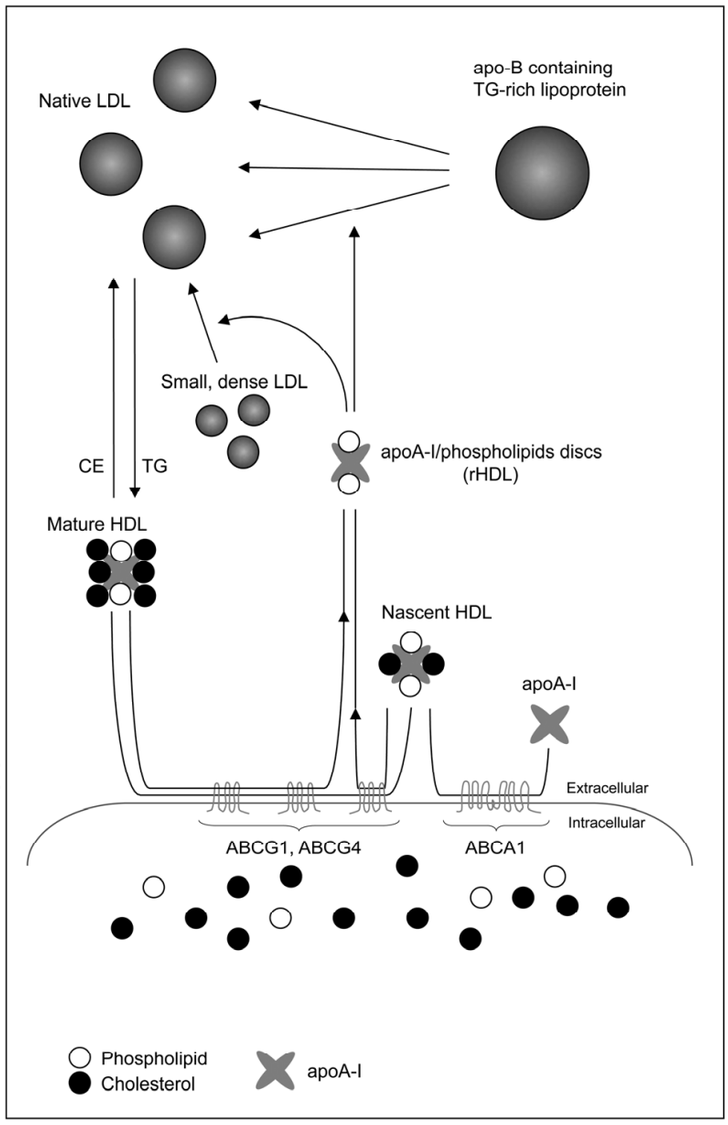



Fig. 6. Suggested function of phospholipid (PL)/apolipoprotein A-I (apoA-I) discs in HDL metabolism. apo, apolipoprotein; rHDL, reconstituted HDL; ABC, ATP-binding cassette transporter; CE, cholesteryl ester; TG, triglyceride

The suggested function of PL apoA-I discs in patients with TD is described in Fig. 6. rHDL and the apoA-I complex with PLs have beneficial effects for cholesterol efflux and lipoprotein components in patients with TD. Briefly, the PL/apoA-I discs acts to modulate lipoprotein metabolism via at least three different steps. 1) PL/apoA-I discs remove the cholesterol from peripheral cells through an ABCA1-independent pathway such as the ABCG1- and ABCG4-dependent pathway. 2) PL/ApoA-I discs form nascent HDL particles with cholesterol and PLs. 3) PL/ApoA-I discs interact with other lipoproteins such as apoB containing TRLs in circulating plasma. The discoidal apoA-I or apoA-I mimetics complex with PLs and potentially prevent or cure the symptoms of TD.

## 7. Conclusion

TD is a rare autosomal recessive disorder characterized by the absence or extremely low levels of HDL cholesterol and apoA-I in plasma. In addition, cholesteryl esters accumulate in many macrophage-rich tissues and organs. TD is caused by a defect in the ABCA1 gene, which is located on chromosome 9q31. ABCA1 has been identified as a pivotal gene in the regulation of plasma HDL cholesterol levels and cellular cholesterol homeostasis, which are defective in patients with TD. ABCA1 is a membrane protein that transports cholesterol and phospholipids from the membranous inner leaflet to the outer leaflet, and subsequently, lipid-free or lipid-poor apoA-I takes up the transported cholesterol and phospholipids to yield nascent HDL. Due to the ABCA1 genetic defect, patients with TD have an extremely low level of HDL cholesterol and cannot form nascent HDL particles. Namely, TD is based on a disorder of cellular cholesterol excretion as the initial step of RCT via ABCA1. If the process is able to performed in vitro, it leads to the generation of HDL particle, which can take up the excessive cholesterol from peripheral cell, and it acts as a new therapeutic target without using gene therapy in patients with TD.

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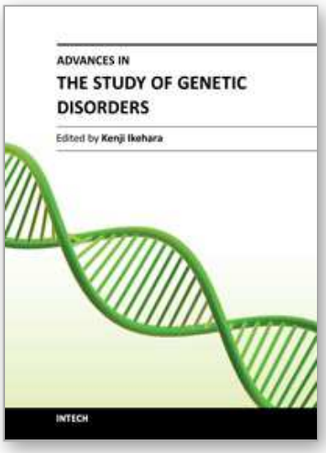
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**Advances in the Study of Genetic Disorders**

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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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