Case Report

A Resuscitated Case of Acute Myocardial Infarction with both Familial Hypercholesterolemia Phenotype Caused by Possibly Oligogenic Variants of the *PCSK9* and *ABCG5* Genes and Type I CD36 Deficiency

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A 56-year-old postmenopausal woman with out-of-hospital cardiac arrest caused by acute myocardial infraction was successfully resuscitated by intensive treatments and recovered without any neurological disability. She was diagnosed as having familial hypercholesterolemia (FH) based on a markedly elevated low-density lipoprotein cholesterol (LDL-C) level and family history of premature coronary artery disease. Genetic testing in her family members showed that a variant of the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene (c.2004C>A, p.S668R), which had been previously reported as having uncertain significance, was associated with FH, indicating that the variant is a potential candidate for the FH phenotype. Next-generation sequencing analysis for the proband also showed that there was a heterozygous mutation of the ATP-binding cassette subfamily G member 5 (*ABCG5*) gene (c.1166G>A, R389H), which has been reported to increase LDL-C level and the risk of cardiovascular disease. She was also diagnosed as having type 1 CD36 deficiency based on a lack of myocardial uptake of ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methyl-pentadecanoic acid in scintigraphy and the absence of CD36 antigen in both monocytes and platelets in flow cytometry. She had a homozygous mutation of the *CD36* gene (c.1126-5_1127delTTTAGAT), which occurs in a canonical splice site (acceptor) and is predicted to disrupt or distort the normal gene product. To our knowledge, this is the first report of a heterozygous FH phenotype caused by possibly oligogenic variants of the *PCSK9* and *ABCG5* genes complicated with type I CD36 deficiency caused by a novel homozygous mutation. Both FH phenotype and CD36 deficiency might have caused extensive atherosclerosis, leading to acute myocardial infarction in the present case.

Key words: CD36 deficiency, Familial hypercholesterolemia, PCSK9, ABCG5

Introduction

Familial hypercholesterolemia (FH) is characterized by a marked elevation of low-density lipoprotein (LDL) cholesterol (LDL-C) level and the presence of premature atherosclerotic coronary artery disease[1]. Genetic mutations associated with metabolism of LDL-C, including loss-of-function mutations in the LDL receptor (*LDLR*) gene, gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene and mutations in the apolipoprotein B (*APOB*) gene, have been reported to cause FH[1]. Genetic testing for FH is useful not only for making a diagnosis but also for risk stratification and prediction of prognosis in each patient[2]. A number of genetic variants of the *LDLR* and *PCSK9* genes have been reported, but pathogenic roles of the variants have not necessarily been demonstrated[2]. In addition, a substantial number of individuals with clinical FH have no causative
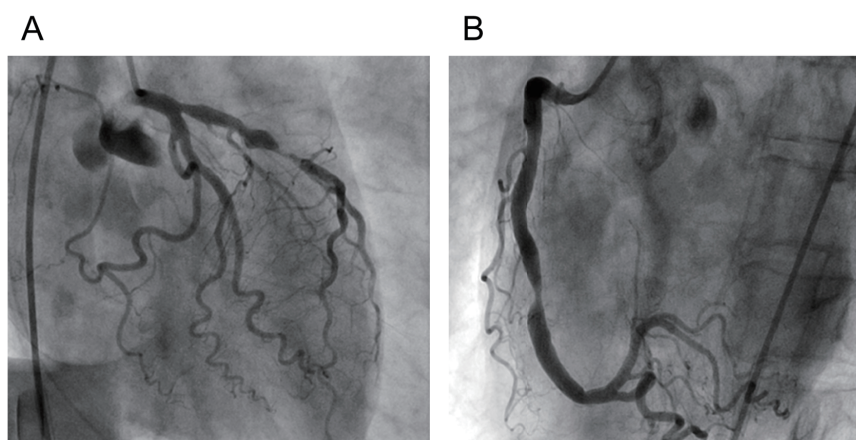
Fig. 1. Coronary angiography

Subtotal occlusion of the left descending artery with ectasia (A) and significant stenosis in the middle of the right coronary artery (B) were observed in the proband.

mutations in the established FH genes[2]. It has been reported that concomitant mutations in accessory genes, including ATP-binding cassette sub-family G member 5 or member 8 (*ABCG5* or *ABCG8*) and apolipoprotein E (*APOE*), contribute to worsening of the FH phenotype, and such a situation has been defined as oligogenic FH[3].

CD36, an 88-kDa glycoprotein, acts as a receptor for oxidized LDL and a transporter of long-chain fatty acids[4]. CD36 is expressed in various human cells including platelets, monocytes/macrophages, capillary endothelial cells, adipocytes, epithelial cells in the kidney and cardiac myocytes[4]. It has been reported that CD36 deficiency is associated with elevation of LDL-C level[5, 6] and severe atherosclerotic cardiovascular diseases, which possibly result from elevated levels of triglycerides, chylomicron remnants and small dense LDL and hepatic insulin resistance induced by accumulation of long-chain fatty acids in the liver[7, 8]. Furthermore, results of an earlier study suggested that reduction in myocardial uptake of long-chain fatty acids due to CD36 deficiency is involved in the pathogenesis of cardiomyopathy, especially hypertrophic cardiomyopathy[9].

Herein we report the first case of a heterozygous FH phenotype caused by possibly oligogenic variants of the *PCSK9* and *ABCG5* genes complicated with type I CD36 deficiency, which might have contributed to extensive atherosclerosis in that case.

Case Report

A 56-year-old postmenopausal and non-obese (body mass index: 19.6) woman with untreated dyslipidemia was admitted to our institute for treatment of out-of-hospital cardiac arrest with ventricular fibrillation. Cardiopulmonary resuscitation including repeated direct current defibrillation failed to restore spontaneous circulation, and venous-arterial extracorporeal membrane oxygenation was therefore commenced. Emergent coronary angiography showed subtotal occlusion of the left descending artery and significant stenosis of the right coronary artery concomitant with diffusely diseased and ectatic coronary arteries **(Fig. 1)**. Percutaneous coronary intervention with stents to the left descending artery lesion was successfully performed, restoring TIMI grade 3 flow. After intensive care including therapeutic hypothermia, she recovered without any neurological disability.

Her untreated LDL-C level was 274 mg/dL in a previous health examination. Laboratory blood tests on day 24 of hospitalization showed an elevated LDL-C level of 195 mg/dL even under treatment with 5 mg rosuvastatin daily, which had been commenced after admission. She also had elevated levels of fasting triglycerides (159–278 mg/dL), remnant-like particle cholesterol (13.3 mg/dL), and malondialdehyde-modified LDL (177 U/L) and increased insulin resistance as assessed by homeostasis model assessment index (HOMA-IR, 3.14) **(Table 1)**. Levels of PCSK9 and sitosterol under the condition of treatment with 20 mg rosuvastatin and 10 mg ezetimibe daily were 138 ng/mL (reference levels in healthy subjects, median [interquartile]: 185 [149-227] ng/mL[10]) and 3.1 µg/mL (reference intervals in healthy female subjects: 1.03-4.45 µg/mL[11]), respectively. Although xanthoma was not observed in Achilles' tendons, of which thicknesses were 5.8 and 4.9 mm in xeroradiography, or the body surface, she had a family

Table 1. Characteristics of the proband's family members

	III-1	III-2	IV-1	IV-2	IV-3
	Proband	Brother	Son	Niece	Niece
Clinical diagnosis of FH	FH	FH	non-FH	non-FH	FH
PCSK9, c.2004C>A, p.S668R	+	+	-	-	+
ABCG5, c.1166G>A, R389H	+				
CD36 (Monocyte, Platelet)	(-, -)	(+, +)	(+, +)		
CD36, c.1126-5_1127del	+ (Homo)				
Xanthoma	none	none	none	none	none
Use of statin	+	+	-	-	-
Lipid-related profile					
Total cholesterol (mg/dL)	270	214	227	198	226
LDL cholesterol (mg/dL)	195	127	157	107	144
HDL cholesterol (mg/dL)	43	65	40	81	56
Triglycerides (mg/dL)	159	110	152	48	131
Apo A-I (mg/dL)	98		142		125
Apo B (mg/dL)	169		121		100
Apo E (mg/dL)	8.6		5.0		3.5
Apo E genotype	$\varepsilon3/\varepsilon3$				
RLP cholesterol (mg/dL)	13.3				4.0
MDA-LDL (U/L)	177				176
Lipoprotein (a) (mg/dL)	58				7
PCSK9 (ng/mL)	138	319	196	103	116
Sitosterol (µg/mL)	3.1				
Glucose metabolism					
Fasting glucose (mg/dL)	120	97	88	113	104
Insulin (µU/mL)	10.6				
Hemoglobin A1c (%)	5.8	5.8	5.2	5.2	5.5
HOMA-IR	3.14				

Apo, apolipoprotein; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; Homo, homozygote; LDL, low-density lipoprotein; MDA-LDL, malondialdehyde-modified LDL; PCSK9, proprotein convertase subtilisin/kexin type 9; RLP, remnant-like particle.

history of premature coronary artery disease; her younger brother (III-2) had a high untreated LDL-C level (>200 mg/dL) and prior percutaneous coronary intervention for unstable angina pectoris at the age of 53 years **(Fig. 2)**. Therefore, the proband (III-1) was diagnosed as having FH according to the criteria of the Japan Atherosclerosis Society[12].

Imaging of fatty acid metabolism using myocardial ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methyl-pentadecanoic acid (^{123}I-BMIPP), a fatty acid analogue, demonstrated a total defect of its uptake in the heart **(Fig. 3A)**, suggesting type I CD36 deficiency[13]. Immunofluorescent flow cytometry confirmed the absence of CD36 antigen in both monocytes and platelets **(Fig. 3B)**. Given these findings, she was also diagnosed as having type I CD36 deficiency. Transthoracic echocardiography showed regional asynergy of the infarcted anterior left ventricular wall but no other abnormalities including

cardiomyopathy. Carotid ultrasonography showed plaque in the left carotid bifurcation but no stenotic blood flow. Computerized tomography showed some areas of calcification in the abdominal aorta.

In addition to her younger brother (III-2), a family screening of FH revealed that her niece (IV-3) also had FH based on a high LDL-C level (144 mg/dL) that met the criteria of the Japan Atherosclerosis Society for pediatric FH[14] **(Fig. 2)**. On the other hand, immunofluorescent flow cytometry analyses showed the presence of CD36 antigen in both monocytes and platelets of her younger brother (III-2) **(Fig. 3B)** and her son (IV-I) **(Fig. 3C)**, indicating that they were not CD36-deficient.

Genetic analysis using Sanger sequencing for FH showed that a variant of the *PCSK9* gene (2004C>A, p. S668R) was present in the three individuals (III-1, III-2 and IV-3) who were diagnosed with FH, but the variant was not found in two other individuals (IV-1
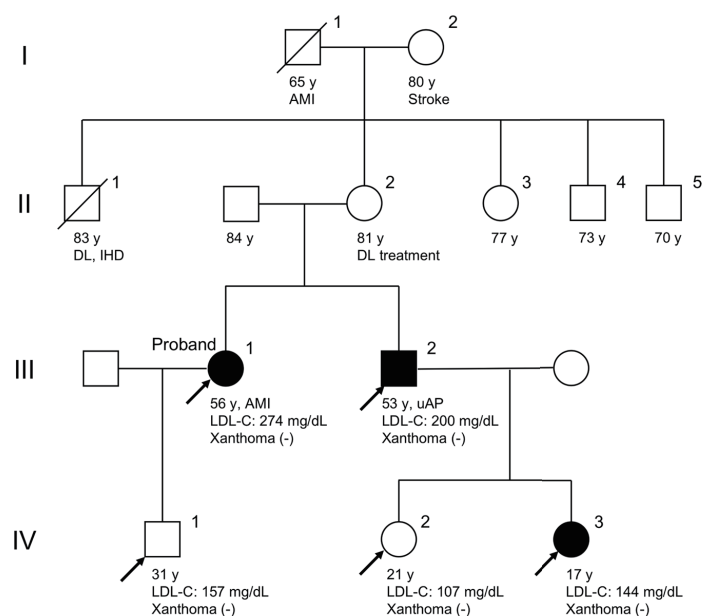
Fig. 2. Pedigree of a family with familial hypercholesterolemia

Squares and circles represent males and females, respectively. Information on age, diagnosis of dyslipidemia (DL) and ischemic heart disease (IHD) including acute myocardial infarction (AMI) and unstable angina pectoris (uAP), untreated low-density lipoprotein cholesterol (LDL-C) level and xanthoma is shown for each individual. The subject who underwent genetic analysis is shown by an arrow. Individuals with and without a variant of the *PCSK9* gene (c.2004C＞A, p.S668R) are shown as filled and open symbols, respectively. A deceased individual is shown as a symbol with a diagonal line. The proband (III-1), her younger brother (III-2) and her niece (IV-3) were clinically diagnosed as having familial hypercholesterolemia (FH) with the *PCSK9* variant, which was thought to be a possibly novel pathogenic variant. The other two individuals, IV-1 and IV-2, who were not clinically diagnosed as having FH did not have the *PCSK9* variant.

and IV-2) who did not meet the criteria for diagnosis of FH **(Fig. 2)**. No mutation of the *LDLR* gene in genetic analyses using the methods of Sanger sequencing and multiplex ligation-dependent probe amplification was found in the family pedigree. Taken together, the findings suggest that this variant of the *PCSK9* gene is a candidate of the heterozygous FH phenotype by a gain-of-function of PCSK9.

Furthermore, next-generation sequencing analysis for the proband showed that there was a heterozygous mutation of the *ABCG5* gene (c.1166G ＞A, R389H), which is associated with sitosterolemia in a homozygous mutation[15] and has been reported to increase LDL-C level and the risk of cardiovascular disease in a heterozygous mutation[16, 17]. There was no pathogenic mutation of the *APOB*, *ABCG8* or *APOE* gene. She also had a homozygous mutation of the *CD36* gene (c.1126-5_1127delTTTAGAT), resulting in type I CD36 deficiency.

After intensive cholesterol-lowering therapy using 20 mg rosuvastatin and 10 mg ezetimibe daily, LDL-C in the present case was decreased to 90 mg/dL at the time of discharge. During a 2-year follow-up period, she had been doing well without any recurrence of cardiovascular events.

Discussion

FH causes premature coronary artery disease because of lifelong exposure to an elevated LDL-C level[1]. The prevalence of FH was reported to be one in 250 individuals in a general population[18], and it was reported to be much higher in patients with coronary artery disease[19]. PCSK9 plays an important role in cholesterol metabolism by regulating the number of cell-surface LDL receptors, and gain-of-function mutations in the *PCSK9* gene cause FH[1]. It has been reported that there are a number of genetic variants of *LDLR* and *PCSK9*, but pathogenic roles of the variants are not necessarily indicated by evidence[2]. The *PCSK9* variant (PCSK9 c.2004C＞A, p.S668R) was first identified in one subject of 3,655 Japanese subjects who underwent sequencing of the promoter and coding regions of the *PCSK9* gene[20] and has been reported as having uncertain significance in the ClinVar database[21]. LDL-C level measured at a single time point was low in the subject with this variant[20], but the possibility of FH in that individual could not be excluded since LDL-C level varies widely even in patients with FH genetic mutations[22]. In the present case, the same *PCSK9* variant (c.2004C＞A, p.S668R)
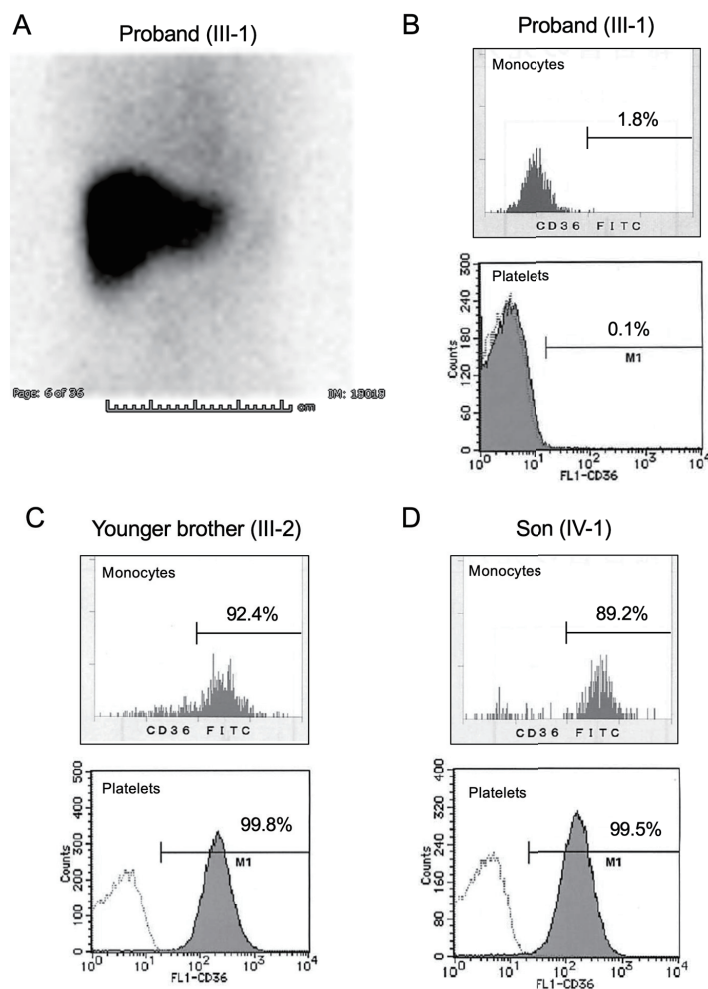
Fig. 3. Diagnosis of CD36 deficiency

The proband (III-1) had a defect in cardiac uptake and an enhanced hepatic uptake of a fatty acid analogue in ^{123}I-BMIPP scintigraphy (A). Immunofluorescent flow cytometry showed the absence of CD36 antigen in both monocytes and platelets of the proband (B). CD36 antigen was detected in both monocytes and platelets of her younger brother (III-2) (C) and her son (IV-1) (D).

was found in three individuals who were clinically diagnosed as having FH but not in two other individuals who were not diagnosed as having FH in a family pedigree. These findings suggest that the variant, PCSK9 c.2004C>A, p.S668R, has gain-of-function of PCSK9 as a cause of FH phenotype. Our previous genetic analyses using 650 probands with FH demonstrated that this variant was present only in the family of the present case, and databases in Japan showed that the allele frequency was 0.03-0.06%[21]. Additional analyses including screening of other family pedigrees are needed to confirm the clinical implications of the variant.

Patients with oligogenic FH were previously defined as those who harbored deleterious variants of both conventional FH genes and LDL-C-altering accessory genes including *ABCG5/ABCG8*[3], which

are associated with sitosterolemia in a homozygous mutation[15]. Rare and deleterious mutations in *ABCG5* and *ABCG8* genes were also reported to mimic and worsen the FH phenotype[16]. Furthermore, it has recently been reported that heterozygous carriers of a loss-of-function variant of the *ABCG5* gene have significantly increased levels of sitosterol and LDL-C and a 2-fold increase in the risk of cardiovascular disease[17]. In the present case, both a variant of the *PCSK9* gene and a pathogenic mutation of the *ABCG5* gene as an accessory gene might contribute to the FH phenotype.

There are two types of human CD36 deficiency, and the prevalences of type I CD36 deficiency, in which neither platelets nor monocytes express CD36, and type II CD36 deficiency, in which monocytes but not platelets express CD36, were reported to be ~1%

and 5.8% of the Japanese population, respectively[23, 24]. The absence of cardiac uptake in ^{123}I-BMIPP scintigraphy is an important finding for diagnosis of type I CD36 deficiency[13], and that was a clue for diagnosis of CD36 deficiency in the present case. Genetic analysis showed a homozygous mutation of the *CD36* gene (c.1126-5_1127delTTTAGAT), which has been reported as having uncertain significance in the ClinVar database. This variant occurs in a canonical splice site (acceptor) and is therefore predicted to disrupt or distort the normal gene product. This is the first case of human type I CD36 deficiency having this novel variant as a homozygous mutation.

Type I CD36 deficiency has been reported to be associated with extensive atherosclerosis and a high incidence of coronary artery disease[8]. As a possible mechanism of the association, induction of insulin resistance and elevation of serum levels of LDL-C and pro-atherosclerotic lipids have been postulated. It has been suggested that human type I CD36 deficiency is associated with insulin resistance[25] and diabetes mellitus[26], major risk factors of atherosclerotic diseases. However, CD36-deficient mice showed enhanced insulin sensitivity in skeletal muscle, while their livers were insulin-resistant with accumulated long-chain fatty acids[27]. In addition, a previous study showed that non-diabetic patients with type 1 CD36 deficiency diagnosed by myocardial ^{123}I-BMIPP scintigraphy were not necessarily insulin-resistant[6]. Therefore, the role of insulin resistance in the association between CD36 deficiency and atherosclerosis in humans remains unclear. On the other hand, CD36 deficiency has been reported to be associated with elevation of LDL-C level[5, 6]. It has also been shown that type I CD36 deficiency increases intake of long-chain fatty acids in the liver and subsequent overproduction of very low-density lipoprotein, resulting in increased levels of triglycerides, APOB-48, chylomicron remnants and small dense LDL[7, 8]. An increase in pro-atherosclerotic lipids may result in exacerbation of atherosclerosis in CD36 deficiency. It has been reported that PCSK9 promotes intestinal overproduction of triglyceride-rich APOB lipoproteins through both LDLR-dependent and -independent mechanisms[28]. Elevation of not only LDL-C but also remnant cholesterol caused by both the FH phenotype associated with PCSK9 and ABCG5 and type I CD36 deficiency might have synergistically contributed to extensive atherosclerosis, leading to acute myocardial infarction in the present case.

To our knowledge, this is the first case report of a heterozygous FH phenotype caused by possibly oligogenic variants of the *PCSK9* (c.2004C>A, p. S668R) and *ABCG5* (c.1166G>A, R389H) genes complicated with type I CD36 deficiency caused by a novel mutation of the *CD36* gene (c.1126-5_1127delTTTAGAT). Detailed family screening was critical for the discovery of a close association of the variant of *PCSK9* gene with FH phenotype. The present case indicates the possibility that both FH phenotype and type I CD36 deficiency synergistically promote the progression of atherosclerosis, leading to severe cardiovascular disease.

Disclosures

None.

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