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Original Article

First case of sitosterolemia caused by double heterozygous mutations in *ABCG5* and *ABCG8* genes

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Abstract: We present the first case of sitosterolemia caused by double heterozygous mutations in ATP-binding cassette subfamily G members 5 and 8 (*ABCG5* and *ABCG8*) genes. A 1-year-old girl was admitted to Kanazawa University Hospital due to her hyper LDL-cholesterolemia (453 mg/dL) as well as intertriginous xanthomas associated with breastfeeding. Initially, she was suspected as familial hypercholesterolemia (FH). However, her LDL cholesterol level significantly reduced after her weaning from breastfeeding. In addition, cascade screening did not show any evidence supporting dominant inheritance pattern as FH. Genetic analyses were performed using custom panel focusing on exome regions of 21 lipid-associated genes, including FH-causing genes (LDL receptor, proprotein convertase subtilisin/kexin type 9, apolipoprotein B), and *ABCG5* and *ABCG8* genes. In addition to a single deleterious mutation in *ABCG5* gene (NM_022436.2:c.1166G>A or NP_071881.1:p.Arg389His), single deleterious mutation in *ABCG8* gene (NM_022437.2:c.1285A>C or NP_071882.1:p.Met429Leu) was also identified. Segregations of those mutations from her parents were confirmed. Her serum sitosterol level was significantly elevated to 15.9 μg/mL, leading to her definite diagnosis as sitosterolemia. The *ABCG5* and *ABCG8* proteins form heterodimers and act as a complex. To the best of our knowledge, this is the first case exhibiting sitosterolemia caused by both *ABCG5* and *ABCG8* gene mutations.
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Introduction

Sitosterolemia (OMIM #210250) characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, resulting in prominently elevated serum levels of plant sterols such as sitosterol and campesterol, has been shown to be caused by mutations in either of two genes, ATP-binding cassette subfamily G members 5 and 8 (*ABCG5* and *ABCG8*).[1,2] Subjects suffering from sitosterolemia primarily present tendinous and tuberous xanthomas and premature coronary atherosclerosis resembling familial hypercholesterolemia (FH).[3–5] We encountered a Japanese girl diagnosed as sitosterolemia caused by double heterozygous mutations in *ABCG5* and *ABCG8* genes using comprehensive genetic analyses for the first time. Cascade screening confirmed the segregations of these mutations from her parents, both of whom exhibited mild elevations of sitosterol levels. The present case provides useful insights into the coordinated function of *ABCG5* and *ABCG8* genes.

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Methods

Study subjects

A 1-year-old Japanese girl was referred to our lipid clinic due to her elevated level of LDL cholesterol without any apparent secondary causes. The initial LDL cholesterol level at the age of one was 453 mg/dL while breastfeeding. Both of her parents showed no evidence of consanguineous marriage, and her older sister was also included in this study. The characteristics of the study subjects are listed in Table 1.

Biochemical analysis

Fasting blood samples were drawn for assays without any lipid-lowering treatments. Serum concentrations of total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and plant sterols were determined as previously described.[6] Apolipoprotein E (ApoE) phenotype was separated by isoelectric focusing and detected by Western blot with ApoE polyclonal antibody (phenotyping ApoE IEF system, JOKOH, Tokyo, Japan).

Genetic analyses

We sequenced the exome region of 21 dyslipidemia-related Mendelian genes, including 3 FH genes (LDL receptor, proprotein convertase subtilisin/kexin type 9 [*PCSK9*], and apolipoprotein B) and *ABCG5* and *ABCG8* genes. Pathogenicity of the variants was determined by the allele frequency, *in silico* annotation tool, and ClinVar. Details are described in Supplemental Material.

Results

Characteristics of study subjects

The initial LDL cholesterol level of the proband was 453 mg/dL during her breastfeeding. Her serum sitosterol level was 15.9 μg/mL. Her parents as well as older sister exhibited mild elevations of serum sitosterol level. In addition, her father exhibited hyper LDL-cholesterolemia as well (Table 1).

Genetic analyses

There are no apparent deleterious mutations in FH-associated genes (LDL receptor, *PCSK9*, and apolipoprotein B) in the proband. However, one mutation known to cause sitosterolemia was found in her *ABCG5* gene (NM_022436.2:c.1166G>A or NP_071881.1:p.Arg389His),[2] and another mutation known to be associated with hyper LDL-cholesterolemia was found in her *ABCG8* gene (NM_022437.2:c.1285A>C or NP_071882.1:p.Met429Leu).[7] These mutations were segregated from her father and mother, respectively (Fig. 1). In addition, her older sister had a single mutation in *ABCG8* gene, segregated from her mother.

Clinical course of the patient

We provided nutrition guidance to the parents after breastfeeding was discontinued, which included low cholesterol (<200 mg daily) and low plant sterol diet (avoiding vegetable oils, nuts and cereals). Her LDL cholesterol level reduced significantly to the normal range after her weaning from breastfeeding in accordance with

Table 1 Characteristics of the family

Subject (gender)	I.1 (Male)	I.2 (Female)	II.1 (Female)	II.2 (Female)
Genotype	W/M1	W/M2	W/M2	M1/M2
Age (y)	36	34	6	1
Total cholesterol (mg/dL)	234	194	190	540
Triglyceride (mg/dL)	130	70	41	236
HDL cholesterol (mg/dL)	42	65	54	40
LDL cholesterol (mg/dL)	166	110	128	453
ApoA-I (mg/dL)	NA	153	148	NA
ApoB (mg/dL)	NA	84	99	NA
ApoE (mg/dL)	NA	4.1	4.1	NA
ApoE phenotype	E3/E3	E3/E3	E3/E3	E3/E3
CETP (μg/mL)	2.9	3.3	3.9	3.2
Sitosterol (μg/mL)	4.5	4.4	4.8	15.9
Lathosterol (μg/mL)	2.2	2.3	1.2	0.7
Campesterol (μg/mL)	7.8	8.1	7.8	19.9
Cholestanol (μg/mL)	2.3	2.9	3.3	4.1

APOB, apolipoprotein B; *APOE*, apolipoprotein E; CETP, cholesteryl ester transfer protein.

Genotype: M1, *ABCG5* (NM_022436.2:c.1166G>A or NP_071881.1:p.Arg389His); M2, *ABCG8* (NM_022437.2:c.1285A>C or NP_071882.1:p.Met429Leu).

Reference ranges of plant sterols: Sitosterol (μg/mL) 1.67–3.13; lathosterol (μg/mL) 2.70–4.50; campesterol (μg/mL) 2.65–4.45; cholestanol (μg/mL) 1.62–3.08.

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