

Sitosterolemia, Hypercholesterolemia, and Coronary Artery Disease

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Sitosterolemia is a rare inherited disease characterized by increased levels of plant sterols, such as sitosterol. The cause of this disease is ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* or *ABCG8*, respectively) gene mutations. Recent advances in genetics have revealed that the prevalence of subjects with deleterious mutations in *ABCG5* and/or *ABCG8* genes could be more than 1 in ~200,000 individuals among the general population. Furthermore, accumulated evidence, including infantile cases exhibiting progression/regression of systemic xanthomas associated with LDL cholesterol levels, have shown that the elevation of LDL cholesterol seems to be the major cause of development of atherosclerosis and not the elevation of sitosterol. Regarding therapies, LDL apheresis, as well as proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitors, could be useful for sitosterolemia, in addition to ezetimibe and/or colestimide. In this study, we provide the current understanding and future perspectives of sitosterolemia, which is currently considered an extremely rare disorder but is expected to be much more prevalent in clinical settings.

Key words: Sitosterolemia, *ABCG5*, *ABCG8*, Familial hypercholesterolemia

Introduction

Familial hypercholesterolemia (FH) is a common inherited disorder of plasma lipoprotein metabolism and is characterized by an elevated level of LDL cholesterol, tendon xanthomas, and premature coronary artery disease¹. The monogenic causes of FH involve gene mutations such as LDL receptor, apolipoprotein B-100, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*)². On the other hand, sitosterolemia (OMIM #210250) is a rare, inherited, autosomal recessive disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, thus resulting in prominently elevated serum concentrations of plant sterols, such as sitosterol and campesterol³. Subjects suffering from sitosterolemia primarily present with tendinous and tuberous xanthomas and premature coronary atherosclerosis, such as FH⁴⁻⁷. LDL cholesterol levels are more variable in sitosterolemia than in other genetic

hyperlipidemias but can be extremely elevated in some patients, particularly in infants; the reason for this phenomenon still remains unclear⁴. This disease is caused by mutations in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*, respectively). In this paper, we provide the current understanding and future perspectives of sitosterolemia, which is currently considered an extremely rare disorder but is expected to be much more prevalent in clinical settings.

Epidemiology

Sitosterolemia is now considered an extremely rare disorder. Approximately ~100 patients have been reported to have sitosterolemia thus far. However, according to The Exome Aggregation Consortium (ExAC) exome browser, 1 in ~220 individuals have loss of function (LOF) mutations in *ABCG5* or *ABCG8* genes⁸; therefore, the rough estimation of the number of pa-

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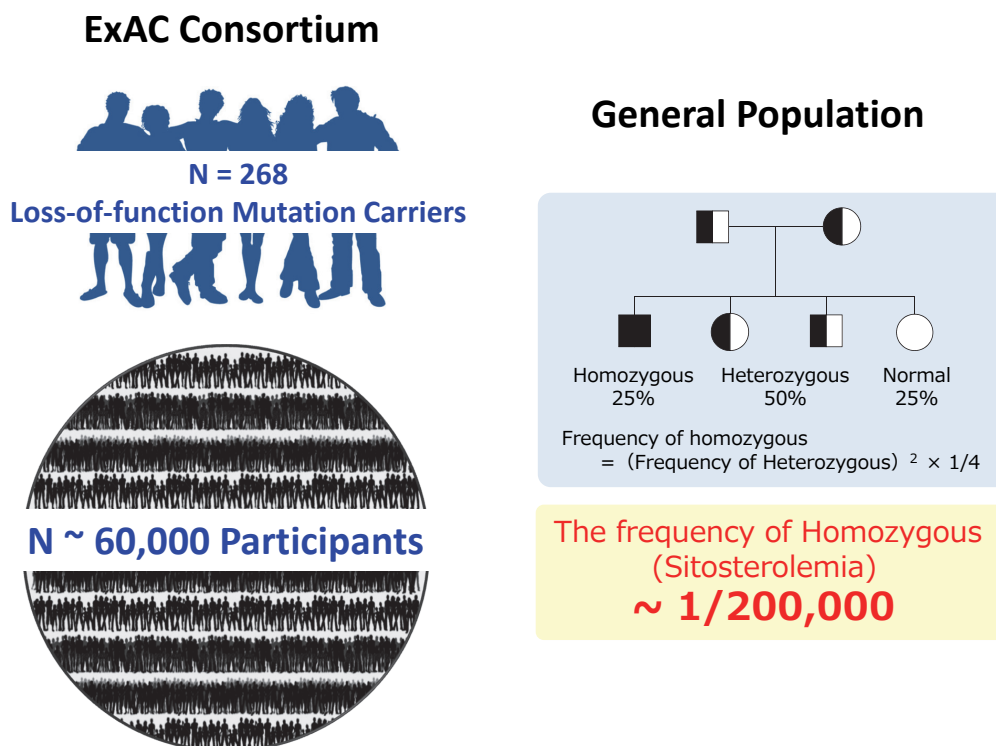


Fig. 1. Assumption of prevalence of sitosterolemia

Left Panel: Among ~60,000 individuals, 268 individuals have LOF mutation(s) in *ABCG5* gene or *ABCG8* gene.

Right panel: According to the frequency of LOF mutation(s) in *ABCG5/8* genes, the frequency of sitosterolemia could be estimated around at least 1 in 200,000.

tients with sitosterolemia is 1 in ~200,000 individuals (**Fig. 1**). In addition to LOF mutations, many missense mutations have also been shown to cause this situation. Moreover, we have already experienced more than 10 Japanese cases thus far⁴⁻⁷. Accordingly, we firmly believe that we have overlooked many sitosterolemic cases because serum sitosterol measurement is not available in most clinics in the world, including Japan. Regarding this important point, Japan Atherosclerosis Society is now investigating the serum sitosterol levels in the general population and the prevalence of sitosterolemia. We anticipate that the measurements of serum sitosterol will be covered by health insurance in Japan in the near future, and such a situation will give us more chances to diagnose this disease accurately.

ABCG5 and ABCG8 Mutations

Most sitosterolemic cases in Asians have been shown to be caused by mutations in the *ABCG5* gene, whereas those in Caucasian are believed to be caused by mutations in the *ABCG8* gene^{9, 10}. However, recent studies, including our previous study, have revealed the causative mutations in the *ABCG8* gene from Asian

sitosterolemic patients⁷. Accordingly, *ABCG8* and *ABCG5* gene mutations should be examined if sitosterolemia is suspected regardless of ethnicity. Furthermore, the *ABCG5* and *ABCG8* proteins form heterodimers and act in coordination as a complex¹¹. We recently observed a sitosterolemia case caused by combinations of *ABCG5* and *ABCG8* gene mutations (data not shown). Moreover, we recently published a paper regarding the prevalence of oligogenic FH with deleterious mutations in FH genes and the *ABCG5/8* genes¹². We found that additional mutation(s) in the *ABCG5/8* genes significantly affected LDL cholesterol level and coronary artery disease prevalence. These findings and a recent study revealed that *ABCG5/8* genetic mutations significantly affected LDL cholesterol levels in the general population; this information supports the notion that there are many heterozygous carriers of this disease among patients with hypercholesterolemia¹³. The mutations that could cause sitosterolemia and polymorphisms are illustrated in **Fig. 2**.

Clinical Manifestations

The variations in phenotypic severities of this

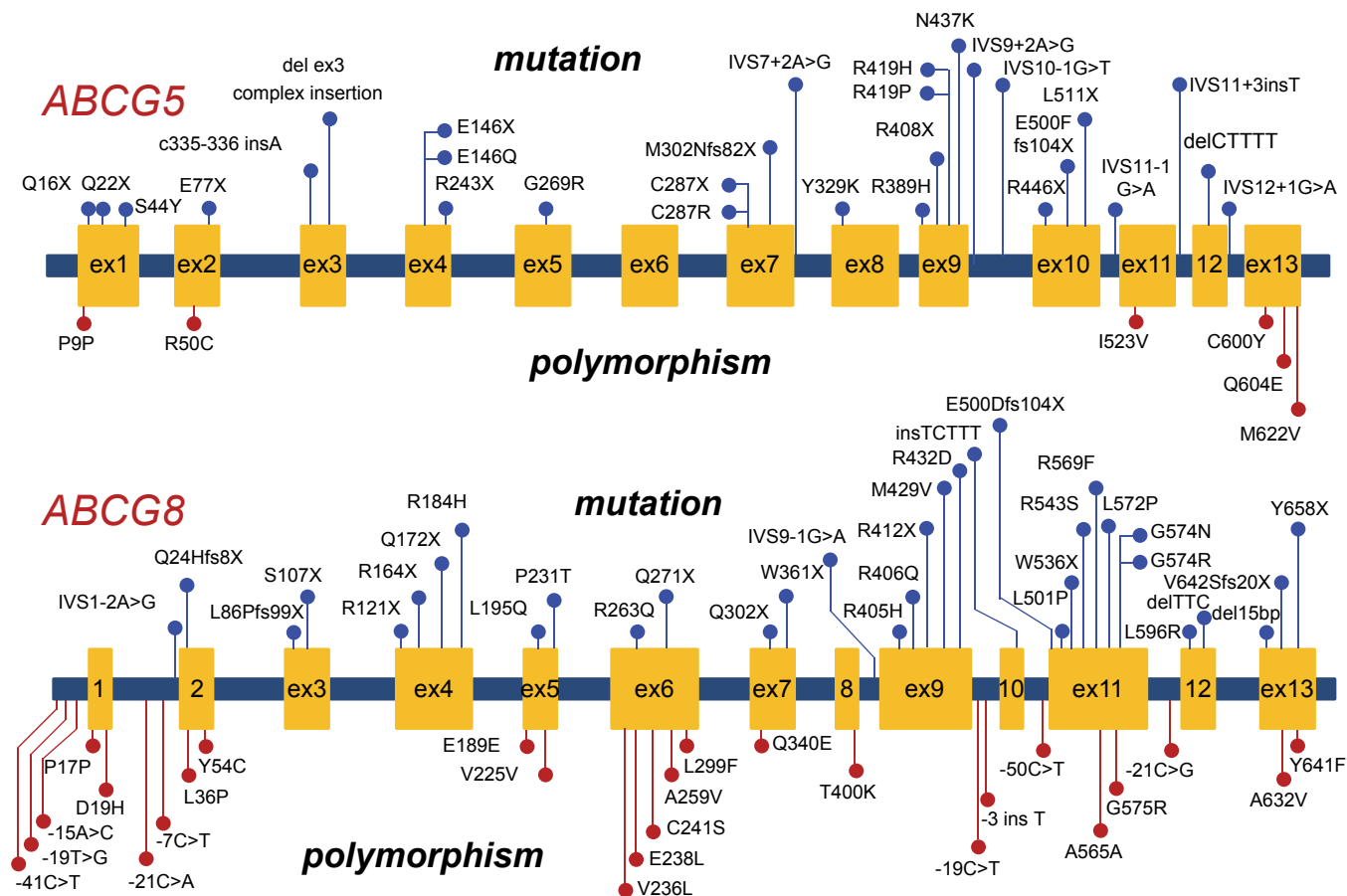


Fig. 2. Mutations and polymorphisms in the *ABCG5* and *ABCG8* genes

Mutations are illustrated as blue. Polymorphisms are illustrated as red.

Upper panel: Mutations and polymorphisms in the *ABCG5* gene.

Lower panel: Mutations and polymorphisms in the *ABCG8* gene.

disease have been reported. We previously described a case with sitosterolemia in a 26-year old lady exhibiting premature myocardial infarction⁷. Other studies have showed sitosterolemic cases without any apparent atherosclerosis¹⁴. Regarding this information, several infantile cases, including ours, have exhibited severe hyper LDL cholesterol during breastfeeding^{4, 10}. Moreover, LDL cholesterol levels in adult sitosterolemic patients are more variable than that in other genetic hyperlipidemias¹⁵. These facts suggest that sitosterolemic patients are vulnerable to diet-induced hyperlipidemia. Thus, we speculated that LDL cholesterol associated with dietary habits significantly affects their clinical manifestations and conducted a single arm, nonrandomized, open-label, uncontrolled trial to determine if postprandial remnant-like particle (RLP) fractions were elevated in this disease¹⁶ We found that postprandial RLP lipoproteins were significantly impaired compared to heterozygous FH¹⁷. Accordingly, we believe that RLP and LDL cholesterol associated

with their dietary habits are quite important for the prevention of atherosclerosis in this disease.

Heterozygous Mutation Carriers

Although sitosterolemia is now considered a “recessive” disorder, recent studies have revealed the fact that heterozygous mutation carriers also exhibit milder manifestations^{18, 19}. We previously showed that a portion of hypercholesterolemia other than FH could be explained by a deleterious mutation in the *ABCG8* gene²⁰. We also showed that single deleterious mutations affected LDL cholesterol levels by 18 mg/dL among individuals exhibiting severe hyper LDL cholesterol¹². Another group showed that a portion of hypercholesterolemia other than FH could be explained by a deleterious mutation in *ABCG5* or *ABCG8* gene¹⁴. These results collectively suggested that heterozygous mutation carriers in the *ABCG5/8* genes could be one of the major genetic causes of hyper



Fig. 3. Physical xanthomas in sitosterolemia

Tendinous xanthomas of the case with sitosterolemia (16-year-old male, Ref. 6)

Achilles' tendon xanthomas with sitosterolemia (16-year-old male, Ref. 6)

Xanthomas at the wrist (1-year-old female, Ref. 4)

Xanthomas at the ankle (1-year-old female, Ref. 4)

LDL cholesterolemia.

Pseudo Familial Hypercholesterolemia

Sitosterolemia has been described as “Pseudo FH,” particularly infant cases, on the basis of phenotype, such as hyper LDL cholesterolemia, as well as tendon xanthomas²¹⁾ (Fig. 3). Previous studies have shown multiple infant cases of sitosterolemia with extreme hyper LDL cholesterolemia associated with breastfeeding^{4,10)}. Interestingly, weaning can reduce their LDL cholesterol level substantially but will not affect their sitosterol level (Fig. 4). The detailed mechanism of this extreme situation is still unclear; however, the disturbance of postprandial remnant lipoprotein fractions seems to be one of the factors that contribute to this situation¹⁷⁾.

Sitosterol or Cholesterol?

Sitosterolemia is known to show elevated sitos-

terol and LDL cholesterol levels. In contrast to LDL cholesterol, the pathogenicity of sitosterol on the development of atherosclerosis still remains unclear. Regarding this point, only a few studies have systematically investigated this issue, and serum sitosterol level itself does not seem to be the causal factor^{22, 23)}. Further studies with larger sample sizes are needed to elucidate this issue. On the other hand, a recent clinical trial has shown that serum sitosterol level could be a good biomarker of ezetimibe efficacy²⁴⁾. Serum sitosterol has been shown as a surrogate marker of cholesterol absorption²⁵⁾. This result may reflect the fact that ezetimibe could be more effective in patients with increased cholesterol absorption due to primary or secondary causes. Accordingly, serum sitosterol measurements could be used not only for the clinical diagnosis of sitosterolemia but also for the prediction of ezetimibe efficacy.

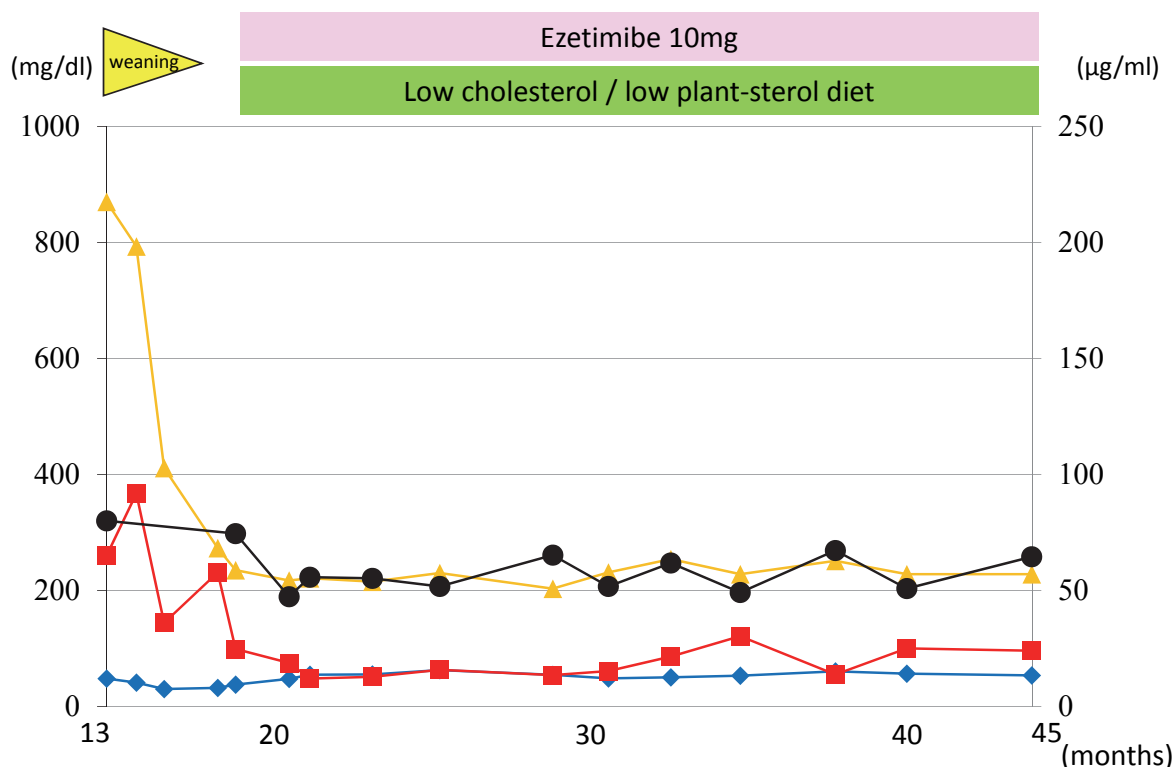


Fig. 4. Representative infantile case with breastfed sitosterolemia

The clinical course of the infantile case with sitosterolemia (13-month-old girl). Closed black circle indicates sitosterol, and closed orange triangle indicates LDL cholesterol. Closed red square indicates triglyceride. Closed blue rhombus indicates high-density lipoprotein cholesterol.

Clinical Phenotypes of Sitosterolemia Other Than Atherosclerotic Disease

It has been shown that some patients with sitosterolemia suffer from hematologic abnormalities, including abnormal erythrocyte shape, thrombocytopenia, and arthritis^{26, 27}. This phenomenon is now being investigated because of the accumulation of elevated plant sterols. However, we previously showed a unique case complicated by arthritis due to a combination disease of sitosterolemia and familial Mediterranean fever, whose typical manifestation includes arthritis⁵. This case shows a recessive disorder that is usually associated with consanguineous marriage; hence, another recessive disorder could occur with these other phenotypes. Comprehensive genetic analysis for such cases should be quite useful for uncovering the potential cause of those situations.

Managements for Sitosterolemia

Several medications for reducing LDL cholesterol and sitosterol have been introduced for sitosterolemic patients^{28, 29}. Among these medications, ezetimibe and

cholestimide have been described as appropriate therapies⁹. It is true that ezetimibe and colestimide are effective in reducing cholesterol and sitosterol, and HMG-CoA reductase inhibitors (statins) are effective in reducing LDL cholesterol in sitosterolemic patients^{28, 30}. In addition to those established approaches, we experienced a sitosterolemia case wherein PCSK9 inhibition had great effect for reducing LDL cholesterol (data not shown). As stated above, the efficacy of reducing sitosterol levels for the prevention of atherosclerosis is still controversial. PCSK9 inhibitors and statins with robust evidence for the reduction of atherosclerotic events could also be considered for patients with sitosterolemia³¹. For patients with advanced atherosclerotic regions, LDL apheresis could be considered if applicable⁶.

Conclusions and Perspectives

It is true that sitosterolemia as a monogenic disorder is rather rare; however, the prevalence of this disorder is currently underestimated. Furthermore, relatives of sitosterolemia patients or those with heterozygous mutation carriers usually exhibit elevated

sitosterol and LDL cholesterol levels. Moreover, such mutations affect the phenotype of FH. Considering the potential mechanism of elevation of such sterols in this situation, including heterozygous mutation carriers, ezetimibe should be the best treatment; however, statins and PCSK9 inhibitors could be considered if the LDL cholesterol level is very high. The evidence suggests that LDL cholesterol rather than sitosterol should be treated despite the name of this disease. The accurate prevalence data of this disease and clinical data from clinical diagnoses supported by health insurance and comprehensive genetic analyses are needed to further elucidate the clinical importance of this disease.

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None

Conflicts of Interest

None

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