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Recent advances in *ABCG5* and *ABCG8* variants

Vincent Fong, **Shailendra B. Patel**

Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati, Cincinnati, OH, USA

Abstract

Purpose of Review: In this review, we summarize the genetics and mechanisms of sitosterolemia and sterol trafficking, and provide an update on the understanding of the prevalence of *ABCG5* and *ABCG8* variants and their role in human disease.

Recent Findings: Defects in ABCG5/G8 result in the accumulation of xenosterols. It had been previously thought that near total loss of function of one of the proteins was required to cause pathology. However, recently there was the first report of a patient with Sitosterolemia who was heterozygous for mutations in both genes. Moreover, large population studies have demonstrated the even simple heterozygous carriers are associated with altered lipid profiles and cardiovascular risk. Broader screening has added to the rapidly growing list of gene variants indicating that the prevalence of *ABCG5/G8* variants is higher than previous thought, especially in patients with hypercholesterolemia.

Summary: These findings support a strategy of measuring xenosterol levels in patients with hypercholesterolemia to screen for *ABCG5/G8* variants, and then tailoring treatment with a sterol absorption inhibitor, like ezetimibe, where indicated. Xenosterol trafficking affects remnant clearance and maybe pathogenically linked to the increased risk of atherosclerosis.

Keywords

sitosterolemia; xenosterols; *ABCG5* ; *ABCG8*

Introduction:

Sitosterolemia is an autosomal recessively inherited rare disease characterized by the elevated plasma levels of plant sterols or non-cholesterol sterols (xenosterols). Sitosterolemia was first described by Bhattacharyya and Connor in 1974 in 2 sisters with signs suggestive of familial hypercholesterolemia (FH), including arthralgias and tendon xanthomas, but not elevated plasma cholesterol levels[1]. Its name is derived from the most abundant plant sterol detected in the original case report, but we now know definitively that all xenosterols can accumulate in this condition and this disease should now be referred to as Xenosterolemia since an array of different xenosterols have been shown to accumulate in affected individuals. The molecular basis for this disease is mutations in either *ABCG5*

*Correspondence to Vincent Fong (fongvt@ucmail.uc.edu) or Shailendra B. Patel (sbpatel@uc.edu), University of Cincinnati College of Medicine, Division of Endocrinology, Diabetes, & Metabolism, 231 Albert Sabin Way, MSB 7168, Cincinnati, OH 45267; Phone 513 588 4444.

or *ABCG8*; ABCG5 and ABCG8 (also known as sterolins) are known to function as obligate heterodimers and expressed only in hepatocytes or enterocytes [2]. The *ABCG5* and *ABCG8* genes are located at the *STSL* locus on chromosome 2p21, arranged about 400bp apart in a head to head configuration[2]. The ABCG5/G8 heterodimer preferentially pumps xenosterols out of enterocytes back into the intestinal lumen and also out of hepatocytes into the bile canaliculi for excretion, resulting in a net absorption of 0.4–2% of xenosterols and ~55% of dietary cholesterol in heathy individuals[3]. However, in patients with sitosterolemia, defects in this efflux pump result in accumulation of xenosterols with plasma levels up to 40-fold higher than in unaffected individuals[3]. It is important to note that cholesterol is also pumped out by these transporters and ABCG5/G8 is the major cholesterol efflux pump for biliary cholesterol excretion and transintestinal cholesterol loss.

Cholesterol in the intestinal lumen competes with xenosterols to be incorporated into bile acid micelles[4], which are then transported from the lumen into enterocytes with the assistance of Niemann-Pick C1-like protein (NPC1L1). In enterocytes, cholesterol is esterified and incorporated into chylomicrons, or loaded into Apo AI-containing HDL for distribution to other areas of the body, with the remaining unesterified cholesterol excreted back to the intestinal lumen by ABCG5/8[*5*]. In hepatocytes, cholesterol arrives via chylomicron remnants or via HDL, and is synthesized endogenously. It then can be incorporated into VLDL for export to peripheral tissues, converted into bile acids, or directly excreted into bile. Xenosterols on the other hand are preferentially exported from enterocytes and hepatocytes by ABCG5/8 with only a small fraction retained[*5*]. The xenosterol excreted in bile may very well compete again for incorporation into micelles, and therefore could potentially impair the absorption of multiple times its own volume in cholesterol. The details of the cellular machinery involved in the transport metabolism of the non-excreted xenosterols are not known, but xenosterol has been observed incorporated as part of a variety lipoprotein particles[6]. Given the structural similarity, they may utilize the same cellular machinery as cholesterol, but this has yet to be clearly demonstrated. Moreover, the clinical importance of xenosterols that are delivered systemically remain an active area of research. Patients with sitosterolemia can provide some insight into these questions.

Patients with Sitosterolemia maybe asymptomatic, or can present with xanthomas, premature atherosclerosis, macrothrombocytopenia, anemia, liver disease, or heart disease[3]. All patients will have elevated xenosterols levels, but the elevation of plasma cholesterol seems to be inversely related to age with perhaps an inflexion point around puberty; very young children show a dramatic hypercholesterolemia which seems to abate in late teenage years and affected adults rarely show any hypercholesterolemia.

Advances in prevalence

In recent years, the application of next generation sequencing[7*], mutational analyses and screening of less common phenotypes[8] has led to a rapid increase in case reports of Sitosterolemia and also of associated gene variants [9–21*]. In many cases, Sitosterolemia is easily misdiagnosed as Familial Hypercholesterolemia (FH), since standard clinical ‘cholesterol’ tests are enzymatic and report all blood sterols as cholesterol. Therefore,

xenosterols need to be measured by GC-MS or HPLC [22]. Brinton *et al.* tested sterol levels in 207,926 blood samples sent by US healthcare providers for lipid measurements, and found that 109 patients (0.05%) had sitosterol levels in the diagnostic range for sitosterolemia (>15.0mg/L), and 358 of 8976 (3.99%) of patients with LDL-C ≥190 mg/dL had sitosterol level >99th percentile[**23**]. Sequencing of the patient with the highest LDL-C level found compound heterozygous mutations in the *ABCG8* confirming a diagnosis of sitosterolemia. In an analogous pediatric study, Lee *et al.* measured sterol levels in 109 normocholesterolemic and 220 hypercholesteremic pediatric blood samples in Korea, and identified 1 normocholesterolemic and 15 hypercholesterolemic children with sitosterol levels greater than 5 standard deviations above the median of the normocholesterolemic group[*24*]. Of these, 3 had sitosterol levels overtly higher than the rest, and DNA sequencing of the 2 patients with the highest sitosterol levels revealed one was compound heterozygous for two different mutations of *ABCG5* and the other was homozygous for a mutation of *ABCG8,* confirming diagnosis of Sitosterolemia. While neither of the study populations of Brinton *et al.* or Lee *et al.* are completely random samplings of the general population (since they were from blood samples obtained for medical reasons), it is likely that this rare disease, once estimated to have a frequency of 1 in 3 million individuals, is over represented in patients with hypercholesterolemia and is more prevalent than previously thought.

Advances in Genetics—The long-standing paradigm was that near total loss of function of ABCG5 or ABCG8 was required to cause Sitosterolemia, since all known cases of Sitosterolemia were homozygous or compound heterozygous defects in either *ABCG5* or *ABCG8*. The elegant crystal structure of the ABCG5/G8 heterodimer has permitted a better understanding of the heterodimer and provided a mechanistic understanding of the structure-function[25]. By inference, loss of 50% of function (in carriers of the mutant allele) was associated with no manifestations of disease and therefore the ‘threshold’ for disease manifestation should be <50% and perhaps even <25%. Complete loss of one whole *STSL* locus seemed not to cause an issue as the knockout mice, generated by the Hobbs laboratory, only manifested xenosterolemia when homozygous for the loss of both loci. However, Tada *et al.* recently reported the first case of patient with one mutation in *ABCG5* and one in *ABCG8* [**26**], each inherited from respective parents. The infant presented with classical pseudo-homozygous familial hypercholesterolemia with an elevated serum LDL-C and intertriginous xanthomas. Genetic profiling found no deleterious mutations in FH-associated genes, but a mutant *ABCG5* allele (encoding for Arg389His) was inherited from her father and a mutant *ABCG8* allele (encoding for Met429Leu) inherited from her mother; biochemical testing confirmed Sitosterolemia. This is remarkable because it means that the patient also has one wildtype *ABCG5* and one wildtype *ABCG8* allele, so theoretically these gene products can dimerize and form a fully functional sterol transporter. While the effects of these mutations on heterodimer assembly is not known, assuming that the resulting mutant and nonmutant proteins are expressed in equal amounts and have equal chances to form heterodimers, about 25% of her assembled ABCG5/G8 heterodimers will be wild-type, yet are not able to prevent accumulation of xenosterols. Based on this, we surmise that more than 25% activity of ABCG5/8 is required to prevent a sitosterolemia phenotype. That fraction could potential be even higher, as it is unclear if the products from

her mutant alleles retain any function. Missense mutations can result in nonfunctional to partially functional proteins. An interesting approach to start addressing this question would be to map the positions of these mutations onto the crystal structure of the ABCG5/ABCG8 heterodimer to help better direct *in vitro* studies[25,27]. With the accumulation now of an ever-increasing database of disease-causing mutations affecting the *STSL* locus, more urgent detailed analyses of how these different mutations may cause defective pump function and quantify the severity of dysfunction are required.

It is becoming clearer that the range of clinically significant changes in sterolin pump function caused by genetic variations at the *STLS* locus may represent a continuous spectrum of functionality; varying levels of xenosterol exposures may manifest with meaningful physiological changes. Family members of Sitosterolemia patients, carrying only one mutant allele, were previously thought to be unaffected. However recent studies by Tada *et al.*[**28**] demonstrated that even heterozygous mutant *ABCG5/8* carriers have effects on lipid profiles, with a specific defect on remnant clearance and may act as modifying factors with other lipid gene disorders. Tada *et al.* studied 487 subjects with clinically diagnosed FH and performed whole exome sequencing on 21 dyslipidemia related genes, including *LDLR*, *APOB*, *PCSK9*, *ABCG5* and *ABCG8*[**28**]. They identified 45 patients with deleterious variants of *ABCG5* or *ABCG8*, 37 of whom did not have a mutation in an FH-related gene. Of those, 2 carried homozygous *ABCG8* mutations and 1 carried compound heterozygous *ABCG5* mutations, suggesting that they were misdiagnosed as having FH, but in fact had Sitosterolemia. Even after excluding those with double mutations, they found that FH patients with deleterious variants of *ABCG5* or *ABCG8* averaged sitosterol levels ~40–60% higher than those who did not, regardless of FH gene mutation status. Interestingly, lathosterol levels were reciprocally lower in these subjects suggesting reduced endogenous cholesterol synthesis. As expected, LDL-C levels were elevated in FH gene mutation carriers, but was even higher in patients with both FH gene mutations and deleterious variants of *ABCG5* or *ABCG8*. They found no additional effect on LDL-C levels associated with *ABCG5* or *ABCG8* variants in patients without FH gene mutations. Despite the elevated LDL-C levels, a multivariate logistical regression analysis did not find an association of *ABCG5/8* mutation status to risk of coronary artery disease (CAD, OR=1.29, p=0.23), but this negative finding may be related to the small sample size or the fact that the study population was clinically diagnosed FH patients who already have increased atherosclerotic risk. A similar study by Reeskamp *et al.* sequencing 3,031 clinical FH patients found 191 *ABCG5/G8* variants, 53 of which were deemed likely pathogenic. However, unlike Tada *et al.* they did not find a significant difference in LDL-C levels in patients with variants in both *LDLR* and *ABCG5/G8*, but it may be due to having lipid data for only a small subset (n=89) of patients[*29*,30].

Relationship to atherosclerotic disease

That genetic variations at the *STSL* locus are associated with CAD has been validated by several genome-wide association studies as well as Mendelian randomization studies. To date, most of these studies have been interpreted as the effect of these variants on cholesterol-related changes; the concept that xenosterols may have independent effects (mediated by altered ABCG5/G8 function) has not gained any traction. Until now.

Helgadottir *et al.* used Mendelian randomization to approach this question; if the genetic risk attributable to variations at the *STSL* locus was primarily accounted for their effect on altering LDL-C (or non-HDL-C), then the proportion of risk would be similar to any other gene that raises the LDL-C to the same extent. They analyzed genetic and lipid data from the Icelandic and Danish population as well as from the UK Biobank, the Global Lipids Genetics Consortium, and the Myocardial Infarction Genetics and CARDIoGRAM Exome datasets to assess the relationship between *ABCG5/8* variants and non-HDL cholesterol (N up to 943,891) and CAD (N up to 147,824 cases and 922,265 controls)[**31**]. They identified 9 novel rare *ABCG5/8* variants and 3 previously reported common variants that were associated with non-HLD-C levels and of those, 5 variants were associated with CAD. The authors calculated genetic risks scores for *ABCG5/8* variants and determined that for every 1 nmol/L of increase in non-HDL cholesterol caused by these variants, the CAD risk was increased 2-fold. However, when they analyzed variants in 'classical' lipid genes (*LDLR, HMGCR, APOB* etc.) for every 1 nmol/L increase in non-HDL-C, they elevated the CAD risk only to about 1.54 fold. They concluded that ~62% of the CAD risk associated with *ABCG5/8* variants is attributable to regulating non-HDL-C, leaving 38% of risk that can be attributed to elevated xenosterol levels. This is the most powerful Mendelian randomization study to show robustly that any elevation in xenosterol trafficking has increased CAD risk.

Using a different strategy, Nomura *et al.* analyzed data from 47 individuals in 9 families with Sitosterolemia and over 386,000 participants from the combined databases of Myocardial Infarction Genetics consortium (MIGen), TruSeq Custom Amplicon target resequencing studies (TSCA) and UK Biobank[**32**]. They found that even heterozygous family members of patients with sitosterolemia had ~3-fold elevated xenosterol (sitosterol and campesterol) levels over unaffected family members, compared to ~20–40-fold elevations in patients with sitosterolemia. Interestingly, they also found that carriers of heterozygous mutations in *ABCG5* demonstrated elevated LDL and total cholesterol levels, but this difference was not significant in carriers of heterozygous *ABCG8* mutations (however, the sample size was much smaller). Similarly, a meta-analysis of large case-control datasets found that rare loss of function (LoF) variants of *ABCG5*, but not *ABCG8*, were associated increased LDL-C and increased risk of CAD; 34 out of 29,321 patients with CAD (0.12%) were identified to be carriers of heterozygous mutations of *ABCG5*, compared to 63 carriers among 357,326 controls (0.018%) for an odds ratio (OR) of 2.06. They further calculated the effect size of *ABCG5* LOF variants on CAD and found that it was consistent with the effect predicted by change in LDL-C.

While Sitosterolemia is known to be associated with premature atherosclerosis [33], these studies are the first to provide evidence that there is risk even for heterozygous carries of *ABCG5/8* variants. These studies have major implications in the management of cardiovascular risk. Statins remain the overwhelming first-line recommendation for treatment of hypercholesterolemia for reduction of cardiovascular risk. However, there remains a portion of the population that does not respond adequately to treatment with statins. These studies support a more personalized approach that includes assessment of xenosterol levels to more fully characterize disease phenotype and direct treatment[*5*]. While it may be cost prohibitive to regularly perform sequencing of *ABCG5* and *ABCG8*,

measuring xenosterol levels can serve as a surrogate marker, as it is now clear that even heterozygous carriers of deleterious *ABCG5/8* variants demonstrate elevated xenosterol levels. Moreover, Tada *et al.* showed evidence that carriers of *ABCG5/8* variants had reduced cholesterol synthesis[**28**]. Patients who exhibit relatively lower baseline cholesterol synthesis and higher absorption have been demonstrated to have poorer response to statin therapy than those with relatively higher baseline cholesterol synthesis[34]. Therefore, these data strongly support the consideration of adding ezetimibe, a NPC1L1 inhibitor, to block dietary and biliary sterol (re)absorption to help mitigate additional cardiovascular risk, especially in those patients with elevated xenosterol levels. Indeed, a sub analysis of the HIJ-PROPER trial found that treatment with pitavastatin and ezetimibe combination significantly reduced the incidence of cardiovascular events in patients with high baseline sitosterol levels, but not in patients with low baseline sitosterol This benefit was greater than predicted by LDL-C reduction alone[**35**]. Similarly, a recent case report and retrospective study demonstrated the effectiveness of ezetimibe treatment in patients with *ABCG5/8* variants[**36**,*37*].

Plant based diets are growing in popularity and plant sterols are endorsed by the American Heart Association (AHA), European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) for LDL-C lowering due to the ability to compete with cholesterol for absorption[6,38,39]. However, all 3 of the studies highlighted above provided evidence that even mildly elevated levels of plant sterols are associated with risk of atherosclerosis, raising questions about the safety of phytosterol supplementation. While it is not clear that these data can be generalized to individuals without *ABCG5/8* variants, these data also demonstrate that carriers of *ABCG5/8* variants are not uncommon. Helgadottir *et al.* shows that the allele frequency of common *ABCG5/8* variants ranging about 5–30% and rare variants up to 0.15%[**31**]. Tada *et al.* reported an *ABCG5/8* variant allele frequency of 4.9%[**28**] and Nomura *et al.* reported a heterozygous carrier frequency of 0.12% for *ABCG5* and 0.15% for *ABCG8*[**32**]. Given the mechanism of ABCG5/8 to regulate sterol absorption, the net effect of the gene variant is likely highly dependent on non-genetic lifestyle factors like diet. Conversely, the health effects of a patient's lifestyle are also strongly affected by genetic background.

Finally, we would like to propose that it is high time the disease Sitosterolemia be renamed Xenosterolemia, as the science base is now robust enough to show that ABCG5/G8 are defenses against all xenosterols and not just sitosterol. This will then allow research to focus on the spectrum of these sterols, rather than a blinkered view focused on sitosterol. Doing so will hopefully lead to greater mechanistic insights of the increased CAD risk posed by dietary xenosterols.

Conclusion:

The study of patients with Sitosterolemia has led to the discovery of ABCG5/G8 and valuable insights into the understanding of cholesterol homeostasis, although details about the trafficking of xenosterols still has not been fully elucidated. Recent studies demonstrated that *ABCG5/G8* variants are more prevalent than previously thought, and that even heterozygous carriers have altered sterol profiles and increased cardiovascular risk.

Measuring xenosterol levels can be used to screen patients with hypercholesterolemia for possible ABCG5/G8 variants, who can then be considered for treatment with ezetimibe in addition to statin. It is not clear what level of risk from xenosterols exists for individuals with normal *ABCG5/G8* function. More research into this is necessary. Until then caution should be used when considering supplementing diets with plant base sterols.

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Key Points:

- Defects in ABCG5/G8 result in the accumulation of xenosterols and sitosterolemia.
- More and more cases of Sitosterolemia and novel variants of *ABCG5* and *ABCG8* are being discovered, including one case who was heterozygous for mutations in both genes.
- Deleterious variants of *ABCG5* and *ABCG8* may be as prevalent 5–30% in the general population
- Even heterozygous carriers of *ABCG5/G8* variants can have elevated xenosterol and LDL-C levels.
- Patients with hypercholesterolemia should be screened for elevated xenosterol levels, and if found treated with ezetimibe, a NPC1L1 inhibitor.