Double Heterozygosity for Variants in *ABCG8* and *ABCG5* and Potential Association with Sitosterolemia

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Background and Significance

Sitosterolemia is a rare autosomal recessive lipid disorder caused by biallelic mutations in the **ABCG5** and **ABCG8** genes, leading to elevated levels of plant sterols (e.g., sitosterol) in the blood. These genes encode sterolin-1 and sterolin-2, ATP-binding cassette transporters responsible for expelling sterols from enterocytes into the intestinal lumen. Mutations result in increased absorption and decreased excretion of sterols, causing hypercholesterolemia, premature atherosclerosis, xanthomas, and hemolytic anemia (Berge et al., 2000).

Management includes dietary modifications to limit plant-based oils, nuts, seeds, and certain shellfish, along with pharmacologic treatment like ezetimibe (10 mg daily), which inhibits intestinal sterol absorption (Farzam & Morgan, 2023). We present the case of an individual with abnormal plant sterol levels and heterozygous variants in both genes. This case supports nascent evidence that double heterozygosity in ABCG5 and ABCG8 could lead to sitosterolemia.

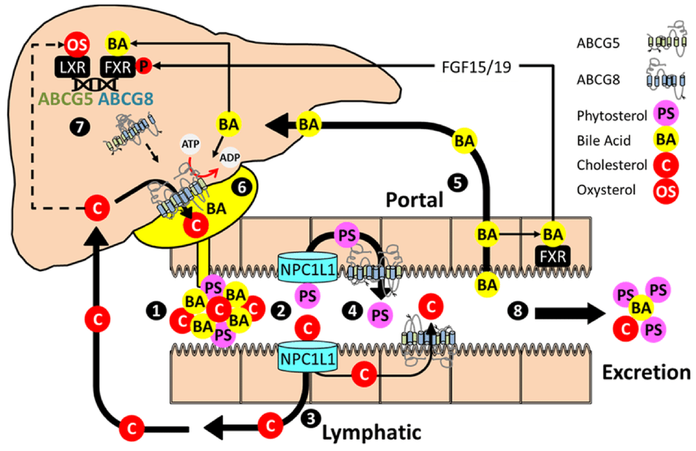

Figure 1. Enterohepatic sterol flux and regulation of ABCG5 ABCG8 (Williams et al., 2021)

Patient History

HPI: A 24-year-old female presented with lifelong gastrointestinal symptoms, syncopal episodes, and atypical lipid profiles. To manage symptoms, she modified her diet over the years, adding nuts, seeds, and plant-based oils, which inadvertently worsened her condition.

PMH: pyloric stenosis, persistent fetal vessel remnant in right eye (confirmed via retinal specialist), pancreatic rest in stomach (confirmed via endoscopy) low ferritin in teens

FH:

Father- systemic mastocytosis, PKD, hypertension, hyperlipidemia, infant jaundice

Mother- polycythemia vera, hypertension, hypercholesterolemia

Genetic Findings

Genetic testing was performed through a direct-to-consumer (DTC) testing platform and results validated through a CLIA-approved laboratory.

ABCG5:Heterozygous variant (rs778605187 G>C). Uncertain significance, associated with sterol metabolism.

ABCG8:Heterozygous variant (rs137852987 G>A). Pathogenic.

Clinical Presentation

Physical Exam: milia in infraorbital region bilaterally, -xanthomas,-arcus senilis

Echocardiogram: Normal structure, EF 66%

Holter Monitor: Sinus rhythm with occasional PVCs and PACs

Lipid Panel and Boston Heart Cholesterol Balance Test:

Before Ezetimibe Treatment	After Ezetimibe Treatment
LDL **125 mg/dL**	LDL **99 mg/dL** (drawn at 6 weeks of treatment)
Lathosterol **76 µmol x 100/mmol**; reference range: 85-125 µmol x 100/mmol	Lathosterol **109 µmol x 100/mmol**; reference range: 85-125 µmol x 100/mmol (16 weeks post-treatment)
Desmosterol **61 µmol x 100/mmol**; reference range: 65-75 µmol x 100/mmol	Desmosterol **71 µmol x 100/mmol**; reference range: 65-75 µmol x 100/mmol (16 weeks post-treatment)
Beta-sitosterol **244 µmol x 100/mmol**; reference range: 115-155 µmol x 100/mmol	Beta-sitosterol **140 µmol x 100/mmol**; reference range: 115-155 µmol x 100/mmol (16 weeks post-treatment)
Campesterol **345 µmol x 100/mmol**; reference range: 170-230 µmol x 100/mmol	Campesterol **187 µmol x 100/mmol**; reference range: 170-230 µmol x 100/mmol (16 weeks post-treatment)
Cholesterol balance score of **0.2** (over-absorber interpretation)	Cholesterol balance score of **0.6** (balanced interpretation) (16 weeks post-treatment)

Management and Treatment

The patient was treated with ezetimibe (10 mg daily) and dietary modifications, resulting in normalized plant sterol levels, reduction in LDL levels, and symptom resolution by the 16-week post-treatment visit.

Conclusions

This case underscores the need for further research into the clinical impact of heterozygous and VUS mutations in ABCG5/ABCG8, particularly in individuals with atypical presentations. It highlights the importance of personalized dietary and pharmacologic interventions in managing sitosterolemia-like syndromes. The findings have implications for the evaluation and management of patients with rare genetic disorders, particularly those involving sterol metabolism.

Additionally, the patient's recurrent gastrointestinal symptoms, a less commonly recognized feature of sitosterolemia, align with a previously reported case of an eight-year-old with similar symptoms that resolved with ezetimibe therapy (Taher et al., 2018). These findings raise the possibility that gastrointestinal manifestations are underdiagnosed or underreported in sitosterolemia-like conditions, particularly in individuals with complex or novel genetic profiles.

This case emphasizes the need for increased awareness among clinicians regarding sitosterolemia and expanded genetic screening to identify and classify VUS mutations.

References

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