Comment on: "Sitosterolemia: Case Series of a Rare Genetic Disorder from India"

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We read with great interest the article by Umapathy and Subbaiah, "Sitosterolemia: Case Series of a Rare Genetic Disorder from India" (JAPI, July 2025;73(7):12–14). The authors deserve appreciation for highlighting this underdiagnosed lipid disorder and for emphasizing the value of peripheral blood smear findings in guiding diagnosis.[1]

We wish to respectfully comment on the next-generation sequencing (NGS) findings, particularly in case 4, where a diagnosis of sitosterolemia was made despite identifying only a heterozygous variant in the *ABCG8* gene. As acknowledged by the authors, sitosterolemia is an autosomal recessive disorder, and clinical disease usually results from biallelic pathogenic variants, either homozygous or compound heterozygous mutations in *ABCG5* or *ABCG8*. A single heterozygous mutation does not typically explain the clinical phenotype and raises important questions:

- Was the variant classified using a recognized variant classification system such as the American College of Medical Genetics and Genomics–Association for Molecular Pathology (ACMG–AMP) guidelines?
- Was it a pathogenic or likely pathogenic variant, or possibly a variant of uncertain significance (VUS)?

Table 1: Typical structured variant report following ACMG-AMP guidelines

Gene (transcript)	*Location*	*Variant*	*Zygosity*	*Classification*
ABCG8 (NM_022437.3)	Exon 5	c.490G>A (p.Arg164His)	Homozygous	Pathogenic

- Was copy number variation (CNV) analysis or deletion/duplication testing performed to identify a second allele that NGS might miss?
- Importantly, plasma plant sterol levels—a biochemical hallmark of sitosterolemia—were not measured. This would have been especially helpful in validating the diagnosis in a borderline genetic case.

For clarity, a typical structured variant report might look like the following (Table 1):

This format illustrates the importance of including transcript IDs, Human Genome Variation Society (HGVS)-compliant variant descriptions, zygosity, and pathogenicity classification using ACMG criteria. Such standardized reporting strengthens diagnostic confidence and clinical utility.[2,3]

We commend the authors for adding to the limited Indian literature on sitosterolemia. However, we suggest that in future publications involving genetic data, key details such as variant classification, evidence of pathogenicity, reporting system used, and whether parental/family segregation or biochemical confirmation was attempted be explicitly mentioned.

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References

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