Sitosterolemia and Anabaptist Groups

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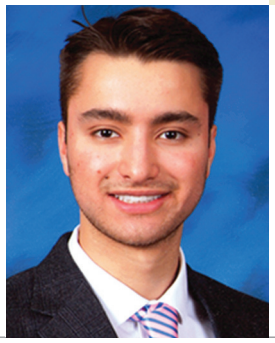

In 1974, Drs. Ashim Bhattacharyya and William Connor described the unusual cases of two sisters of German and German-Swiss background presenting with tuberous and tendon xanthomas of the knees, feet, and hands.[1] In addition to xanthomatosis, these sisters displayed only one other significant abnormality: the presence of high concentrations of plant sterols both in the bloodstream and in the aforementioned xanthoma lesions. Although the human diet includes a substantial amount of various plant sterols, a group of cholesterol-like, four-ringed organic compounds, these sterols are normally found only in trace amounts in the bloodstream and are not synthesized endogenously by animals. Bhattacharyya and Connor named the disease "beta-sitosterolemia" based on the predominant plant sterol found in the patients' blood, and they suggested its genetic origin as a recessively inherited disorder.

Seven years later, a group of investigators from Johns Hopkins University, the University of Oregon, and McGill University reported a case of sudden death from coronary atherosclerosis in a 13-year-old boy from an Amish family in Lancaster County, Pennsylvania.[2] Five of the proband's siblings displayed similar elevations in plant sterols and xanthomatosis, leading the investigators to conclude that sitosterolemia affected the family, and adding to two other isolated case reports from the United States and Europe that had been published since the first report.[3,4] In 1997, sitosterolemia also appeared in the Hutterites, a communal group in North America with Germanic Anabaptist roots like the Amish and Mennonites. This was a case of sudden death due to coronary artery disease[5,6] in a 5-year-old girl from a Canadian Hutterite community. The proband, two siblings, and a first cousin displayed marked elevations in plasma sitosterol, mirroring the Amish family described above.

Molecular genetic assays of individuals clinically affected by sitosterolemia eventually yielded insight into two genes, ABCG5 and ABCG8, that are involved in the regulation of sterol absorption and excretion. Biallelic loss-of-function mutations in either gene prevents the normal function of a heterodimer transporter responsible for limiting the absorption of sterols in the small intestine as well as promoting their excretion into bile.[7,8,9] The disease was, and is at present, thought to appear extremely rarely in the general population, with approximately 100 cases reported worldwide.[10] Cases of phenotypic sitosterolemia among those of Amish-Mennonite background have historically resulted from a single missense mutation in ABCG8 known as G574R (rs137852988) associated with a common haplotype as reported in several index cases.[11] Interestingly, present-day German-Swiss carriers of the ABCG8 G574R also appear to carry the same haplotype, which supports the theory that the Amish-Mennonite carriers are a "founder population" of Swiss origin related to sitosterolemia, and provides the first direct evidence linking contemporary German-Swiss and Amish-Mennonites affected by the same genetic disorder.[12] Furthermore, a population genotyping study performed by the Amish Research Clinic in Strasburg, Pennsylvania, reported a 0.76% allele frequency for the ABCG8 G574R variant among Amish participants, a prevalence approximately 80 times that within the general European population.[13,14]

Population sampling has suggested that the Hutterites display even higher carrier rates of sitosterolemia than do the Old Order Amish, an effect also attributed to the small size of the founding Hutterite population of fewer than 90 individuals. However, genotyping of Hutterite individuals affected by sitosterolemia and their relatives has shown the responsible mutation not to be that affecting the Amish population, G574R, but instead an early-termination mutation known as S107X (rs137854891).[15] Although the Amish and Hutterites are indeed both German-dialect-speaking Anabaptist groups, the elevated prevalence of sitosterolemia among the two groups appears to have occurred through parallel genetic "founder effects" leading to strikingly similar clinical cases of an otherwise extremely rare disease. While counterintuitive, the distinctly separate founder effects thought to be

responsible for elevated prevalence rates of sitosterolemia in the two Anabaptist groups have their roots in the groups' independent histories. The Hutterite sect, taking its name from Anabaptist leader Jakob Hutter, originated in Austria in the 16th century and moved several times to different locations within Europe and the Ukraine to escape religious oppression, establishing settlements and periodically interacting with other Anabaptist groups. They migrated to North America near the end of the 19th century, whereas the initial Amish transatlantic migration began over a century earlier.[16,17]

Studies of sitosterolemia in people of Germanic Anabaptist descent have yielded invaluable insight into the physiological mechanisms and genetic bases of sterol absorption, excretion, and homeostasis. In the 16 years since the first description of ABCG8 in individuals with sitosterolemia, nearly 500 peer-reviewed articles related to the gene have been indexed in the U.S. National Library of Medicine PubMed database.[18] Furthermore, as represented by the case of sitosterolemia in Anabaptist groups, the vast potential that genetic research offers to advance medical knowledge inevitably intersects with history, culture, and shared identity. A complete perspective therefore depends on seeking to understand not only the complex diversity of the human body, but also that of the human condition.

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REFERENCES

1. Bhattacharyya AK and Connor WE. β-Sitosterolemia and Xanthomatosis: a newly described lipid storage disease in two sisters. Journal of Clinical Investigation. 1974;53:1033-1043.
2. Kwiterovich PO, Smith HH, Connor WE, et al. Hyperapobetalipoproteinemia in two families with xanthomas and phytosterolaemia. The Lancet. 1981;317:466-469.
3. Shulman RS, Bhattacharyya AK, Connor WE, et al. Beta-sitosterolemia and xanthomatosis. N Engl J Med. 1976;294:482-3.
4. Miettinen TA. Phytosterolaemia, xanthomatosis and premature atherosclerotic arterial disease: a case with high plant sterol absorption, impaired sterol elimination and low cholesterol synthesis. Eur J Clin Invest. 1980;10:27-35.
5. Wang J, Joy T, Mymin D, et al. Phenotypic heterogeneity of sitosterolemia. J Lipid Res. 2004;45:2361-7.
6. Mymin D, Wang J, Frohlich J, et al. Aortic Xanthomatosis With Coronary Ostial Occlusion in a Child Homozygous for a Nonsense Mutation in ABCG8. Circulation. 2003;107:791-791.
7. Berge KE, Tian H, Graf GA, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science. 2000;290:1771-5.
8. Graf GA, Yu L, Li W-P, et al. ABCG5 and ABCG8 Are Obligate Heterodimers for Protein Trafficking and Biliary Cholesterol Excretion. Journal of Biological Chemistry. 2003;278:48275-48282.
9. Brown JM and Yu L. Opposing Gatekeepers of Apical Sterol Transport: Niemann-Pick C1-Like 1 (NPC1L1) and ATP-Binding Cassette Transporters G5 and G8 (ABCG5/ABCG8). Immunology, endocrine & metabolic agents in medicinal chemistry. 2009;9:18-29.
10. Kidambi S and Patel SB. Sitosterolaemia: pathophysiology, clinical presentation and laboratory diagnosis. Journal of clinical pathology. 2008;61:588-94.
11. Lee M-H, Lu K and Patel SB. Genetic basis of sitosterolemia. Current opinion in lipidology. 2001;12:141-149.
12. Solca C, Stanga Z, Pandit B, et al. Sitosterolaemia in Switzerland: molecular genetics links the U.S. Amish-Mennonites to their European roots. Clin Genet. 2005;68:174-8.
13. Horenstein RB, Mitchell BD, Post WS, et al. The ABCG8 G574R Variant, Serum Plant Sterol Levels, and Cardiovascular Disease Risk in the Old Order Amish. Arteriosclerosis, thrombosis, and vascular biology. 2013;33:10.1161/ATVBAHA.112.245480.
14. Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [July 28 2016].
15. Chong J, Ouwenga R, Anderson R, et al. A Population-Based Study of Autosomal-Recessive Disease-Causing Mutations in a Founder Population. American Journal of Human Genetics. 2012;91:608-620.
16. Hofer A and Hofer N. History of the Hutterite Mennonites. Eugene, OR: Wipf & Stock Publishers; 2011.
17. Nolt S. A History of the Amish: Third Edition: Skyhorse Publishing Company, Incorporated; 2016.
18. PubMed Database. 2016.

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