

Review of: "MTHFR and LC, CFS, POTS, MCAS, SIBO, EDS: Methylating the Alphabet"

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Potential competing interests: No potential competing interests to declare.

The manuscript provides a comprehensive exploration of the connections between Long Covid, Chronic Fatigue Syndrome (CFS), Postural Orthostatic Tachycardia Syndrome (POTS), Mast Cell Activation Syndrome (MCAS), Small Intestine Bacterial Overgrowth (SIBO), and Ehlers-Danlos Syndrome (EDS). The author emphasizes the role of methylation and epigenetic factors, particularly the MTHFR gene and its variants, in determining the phenotypic expression of these syndromes. The folate and methionine cycles are highlighted as primary determinants of epigenetic control, influenced by MTHFR, and are crucial for optimal methylation and epigenome regulation. Additionally, the author underscores the importance of active forms of vitamin D and vitamins B2, B3, B6, B9, and B12 in facilitating optimal methylation and controlling the epigenome. One impressive proposition of the manuscript is the potential link between the female preponderance in these conditions and estrogen's influence on COMT/DAO/MAO activity and IFN- γ production. Despite these commendable aspects, the manuscript has its drawbacks, as pointed out by other reviewers. Its coverage of a broad range of topics may lead to confusion and makes it challenging for readers to focus on the most relevant information and experimental evidence. Nevertheless, the manuscript offers significant contributions and valuable insights. Addressing the concerns raised by reviewers and refining the focus could further enhance the impact of this study.