Insights into Pathophysiological Pathways in ME/CFS Through Genetic Correlation and Mendelian Randomization

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Short Report

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-acute infection syndromes (PAIS) are multisystem disorders involving immune, vascular, neuroinflammatory, and metabolic abnormalities, yet the causal relevance of these processes remains unclear. Using genome-wide summary statistics from DecodeME (15,579 cases), we performed genetic correlation, pleiotropic heritability, and Mendelian randomization analyses.

Across 22 auxiliary traits spanning five mechanistic domains, cellular energetics, neurovascular regulation, and barrier–microbiome function showed the strongest genetic overlap with ME/CFS, with migraine and irritable bowel syndrome contributing most to shared pleiotropy. Immunothrombotic related and inflammatory traits showed smaller but measurable genetic correlations. Energetics-related traits, including type 2 diabetes and blood lactate, displayed consistent genetic correlation but relatively low shared pleiotropy, suggesting that metabolic dysfunction may act through broader physiological networks.

Mendelian randomization identified three biomarkers with evidence for causal effects on ME/CFS risk: higher mitochondrial DNA copy number was protective, whereas increased glycoprotein acetyls and mean platelet volume increased risk. Together, these findings indicate that ME/CFS susceptibility reflects interacting pathways involving barrier–microbiome dysfunction, neurovascular instability, inflammation, platelet activation, and impaired cellular energetics

Main Text

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-acute infection syndromes (PAIS) represent heterogeneous, chronic, and debilitating conditions, with over 60% of long COVID patients meeting diagnostic criteria for ME/CFS(1), indicative of overlapping pathology. Multiple biological domains including immune dysregulation, neuroinflammation, vascular dysfunction, and impaired cellular energetics interact in complex ways, obscuring causal relationships(2). Identifying genetic contributors is therefore critical for establishing mechanistic clarity, informing biomarker development, and guiding therapeutic discovery(3, 4). Large-scale genome-wide summary statistics from DecodeME enable dissection of the genetic architecture of ME/CFS and PAIS (5). Here, we use genetic correlation and causal inference approaches to test a set of mechanistic hypotheses previously supported by biological and clinical evidence linking these processes to ME/CFS and PAIS. The mechanistic domains considered included inflammation, neuroimmune regulation, barrier–microbiome function, vascular regulation, cellular energetics, and platelet-mediated immunothrombosis (6–10). This approach enables a first robust genetic evaluation of candidate biological mechanisms underlying ME/CFS and PAIS, highlighting causal pathways that may inform biomarker discovery and therapeutic targeting.

Materials and Methods

We analyzed genome-wide association study (GWAS) summary statistics from DecodeME together with publicly available GWAS of auxiliary traits (Online Methods). Analyses were restricted to European-ancestry HapMap3 variants using standard LDSC preprocessing. We selected auxiliary traits to represent mechanistic domains repeatedly implicated in ME/CFS, including inflammation, neuroinflammation and immune dysregulation, barrier–microbiome function, vascular/perfusion control, platelet-mediated immunothrombosis, and cellular energetics. Detailed methods and full results are provided in the Online Methods and via a publicly available repository (14).

Results & Discussion

Inflammation. Focusing on innate immune activity, we used blood monocyte count and Glycoprotein acetyls (GlycA) as broad, well-powered proxies of low-grade systemic inflammation. Both traits showed significant positive genetic correlation with ME/CFS, supporting the involvement of chronic inflammatory processes.

Neuroinflammation and immune dysregulation/autoimmunity. To capture sleep–autonomic and neuroimmune regulation, we included insomnia and morning cortisol as proxies of HPA-axis involvement. Both traits showed positive genetic correlation with ME/CFS, with insomnia reaching strong significance ($r_g = 0.243$, $p = 8.4\times10^{-13}$, Fig. 1A). Their PHBC patterns were similar: each showed measurable single-trait pleiotropy with ME/CFS, yet removing either trait from the multi-trait model produced only a modest reduction in shared pleiotropic heritability, as PHBC estimates the proportion of heritability shared across traits(11). This indicates that the neuroimmune and autonomic processes indexed by these proxies are largely captured through covariance with other auxiliary traits rather than representing pleiotropic pathways uniquely tied to insomnia or cortisol (Fig. 1B). Across adaptive and autoimmune traits, systemic lupus erythematosus (SLE) demonstrated the strongest association with ME/CFS ($r_g = 0.200$, $p = 1.15\times10^{-10}$), with multiple sclerosis (MS) showing a smaller but consistent pattern. For both traits, the leave-one-out results indicated that the shared genetic architecture is broadly distributed across related immune traits rather than being isolated to any single autoimmune pathway. As a control for general neurodegeneration, Alzheimer's disease showed no genetic correlation with ME/CFS and minimal single-trait pleiotropy. However, removing it from the full PHBC model reduced the overall estimate of shared pleiotropy, suggesting that Alzheimer's contributes indirectly through its covariance with other auxiliary traits, rather than reflecting mechanisms specific to ME/CFS.

Barrier–microbiome. Given well-established links between epithelial stress, microbial translocation, and gut–brain signaling (5), we used IBS as a clinical proxy for barrier and microbiome dysfunction. IBS showed the strongest evidence for shared genetic architecture with ME/CFS, consistent across both LDSC ($r_g = 0.527$, $p = 2.23\times10^{-27}$) and PHB-C analyses. The drop in shared pleiotropy when IBS was removed indicates that barrier–microbiome processes form a distinct pleiotropic axis not captured by

autoimmune or vascular traits (Fig. 1B). Ulcerative colitis showed a weaker but coherent signal, whereas Crohn's disease displayed a weaker, non-significant overlap.

Perfusion & vascular regulation. To evaluate vascular contributions relevant to postural orthostatic tachycardia syndrome (POTS)-like physiology, we examined proxies of cerebral blood flow and systemic perfusion instability. Migraine, a common comorbidity of POTS reflecting impaired neurovascular reactivity (10), showed a clear positive genetic correlation with ME/CFS ($r_g = 0.45$, $p < 10^{-6}$). PHBC analyses mirrored this result: migraine exhibited substantial single-trait shared pleiotropy with ME/CFS, and its removal from the multi-trait model produced a marked reduction in shared pleiotropy, indicating that neurovascular dysregulation represents a key pleiotropic axis underlying ME/CFS risk. White matter hyperintensity (WMH) volume was uncorrelated, suggesting structural damage is likely secondary rather than causal. Orthostatic hypotension, capturing systemic hemodynamic control relevant to POTS, showed a similar but non-significant positive trend. Although orthostatic hypotension showed high single-trait pleiotropy, removing it did not reduce shared pleiotropy, indicating its signal is captured by traits such as migraine and metabolic proxies. Along with the null result for varicose veins, which represent the structural venous end of this physiology, these findings support a model in which impaired perfusion control stems primarily from functional rather than structural vascular mechanisms in ME/CFS.

Platelets and immunothrombosis. To explore the hypothesis that platelet hyperactivation contributes to endothelial activation and microvascular dysfunction, we used mean platelet volume (MPV) as a proxy for platelet reactivity. ME/CFS showed a small but significant positive genetic correlation with MPV, consistent with a prothrombotic or platelet-primed phenotype suggested for PAIS. As a proxy for downstream endothelial activation and immunothrombosis, venous thromboembolism (VTE) showed a higher and significant correlation with ME/CFS, whereas von Willebrand factor (vWF), despite its correlation with VTE, showed no direct genetic overlap. PHBC analyses showed low single-trait pleiotropy for VTE, MPV and vWF, with little reduction when either trait was removed.

Cellular energetics. To assess genetic contributions to impaired energy metabolism, we examined type 2 diabetes (T2D) and total triglycerides as proxies of systemic metabolic inflexibility. Both traits showed strong positive genetic correlation with ME/CFS (T2D $r_g = 0.15$, $p = 3\times10^{-10}$), indicating a shared predisposition to reduced oxidative capacity. In line with this, blood lactate levels, a product of anaerobic glycolysis, also correlated positively ($r_g = 0.15$, $p = 4.8\times10^{-4}$), reflecting a biochemical shift toward glycolytic energy production when oxidative metabolism is constrained. The PHBC results only partially mirrored these correlations. T2D and lactate each showed relatively low single-trait pleiotropy with ME/CFS, and removing T2D from the multi-trait model produced virtually no reduction in shared pleiotropy, suggesting that its genetic overlap with ME/CFS is largely captured by other traits in the analysis. In contrast, removing lactate notably reduced shared pleiotropy, consistent with a pleiotropic axis related to altered energy metabolism. Although mitochondrial DNA copy number (mtDNA-CN) showed no genome-wide correlation with ME/CFS, it represents a proxy for mitochondrial biogenesis and integrity and is a core determinant of cellular energy supply. The strong genetic correlations of

energetics-related traits with ME/CFS suggest that energetic constraints represent a key pathophysiological feature shared across ME/CFS and PAIS, underscoring post-exertional symptom exacerbation (PEM) as the clinical hallmark of these disorders.

Long COVID. Overall, the Long COVID GWAS summary statistics (13) showed genetic correlations with the same direction and comparable magnitude as those observed for ME/CFS across most traits. In some domains, such as migraine, insomnia, and rheumatoid arthritis the correlation coefficients were even higher than for ME/CFS, yet none reached statistical significance, reflected by low z-scores and smaller squares in Fig. 1. This lack of significance likely reflects increased variance due to smaller case numbers, phenotypic heterogeneity, or ancestry differences. Consequently, several traits showed reversed correlation directions, most plausibly reflecting dataset variance rather than biological divergence.

Mendelian randomization (MR). Whereas LDSC and PHB-C quantify shared genetic architecture, Mendelian randomization (MR) enables causal inference by using genetic variants as natural experiments. Conceptually, MR resembles a randomized controlled trial: individuals who carry genetic variants that increase an exposure (e.g., platelet activity or mitochondrial DNA copy number) are analogous to participants randomized to the “intervention” arm, whereas non-carriers act as the “control” group. Because genotypes are assigned at conception and not influenced by disease processes, MR can provide evidence for directional, potentially causal effects under appropriate assumptions (13). We restricted MR analyses to biomarker traits. Of the nine biomarkers tested, three showed evidence of a causal relationship with ME/CFS in the primary inverse-variance weighted (IVW) analysis. Higher mitochondrial DNA copy number was associated with a lower risk of ME/CFS (OR ≈ 0.83 per SD increase), consistent across multiple sensitivity analyses (Fig. 2). In contrast, higher glycoprotein acetyls, a marker of chronic inflammation, increased ME/CFS risk (OR ~ 1.12). Mean platelet volume also showed a positive causal effect (OR ≈ 1.09), supporting a role for platelet activation in ME/CFS pathophysiology. No significant causal effects were observed for lactate, triglycerides, vWF, or monocyte count. Full sensitivity analyses, heterogeneity estimates, and reverse-direction MR results are provided in a publicly available repository (14).

Limitations of study

Several limitations should be considered when interpreting these findings. First, although LDSC and PHBC provide robust estimates of genetic correlation and shared heritability, both methods rely on additive polygenicity and therefore cannot capture nonlinear or interactive biological processes that are likely relevant to ME/CFS pathophysiology. Second, many auxiliary traits represent imperfect biological proxies, for example, IBS for epithelial–microbiome dysfunction or migraine for impaired neurovascular reactivity, which constrains domain specificity. Third, the Long COVID summary statistics, while invaluable, are limited by smaller sample sizes and phenotypic heterogeneity, which may increase statistical variance and reduce power to detect significant genetic correlations. Fourth, Mendelian randomization analyses depend on strong instrument validity and are susceptible to horizontal

pleiotropy, particularly for highly interconnected immune and metabolic biomarkers. Taken together, these limitations suggest that our results should be interpreted as identifying broad mechanistic domains rather than isolated causal pathways, providing a foundation for more targeted analyses as additional domain relevant GWAS become available

Declarations

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Data Availability

All data used in this study are publicly available. Genome-wide association study summary statistics were obtained from published sources. All analysis outputs, and reproducible code are archived on Zenodo at https://doi.org/10.5281/zenodo.18198370 The analysis pipeline and source code are also available at https://github.com/Mwielscher/pleioh2g_MECFS

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