Plan Overview

A Data Management Plan created using DMPTool

Title: Identifying epigenetic determinants of ME/CFS using plasma cell-free DNA

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Project abstract:

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a heterogeneous, disabling, and debilitating disease with unknown origin. There are no biomarkers available to diagnose ME/CFS to date. Despite multiple trials of therapeutic interventions, no effective treatment is presently available. Therefore, there is an urgent need to develop novel biomarkers and therapeutic targets to address the burden of this disease. Epigenetic dysregulation has been implicated in many diseases, including ME/CFS. However, few epigenetic studies have been directed to ME/CFS in peripheral blood mononuclear cells (PBMCs). DNA methylation studies of ME/CFS using whole genome bisulfite sequencing (WGBS) have not been reported in ME/CFS patients. DNA methylation profiling using cell-free DNA (cfDNA) holds promise as a potential approach for liquid biopsy applications to establish consistent diagnostic and prognostic markers. In this study, we propose to carry out WGBS on the plasma of ME/CFS patients and healthy controls (HC) to identify novel genes that could potentially be developed into minimally invasive biomarkers.

Relevance to topic area: This proposal is intended to identify epigenetic dysregulations in ME/CFS that align exactly with the topic area under the portfolio category of Neuroscience. Similarly, the goal of the proposal is identifying epigenetically dysregulated genes and developing them into a panel of molecular biomarkers to improve ME/CFS diagnostic testing and clinical decision making. Therefore, this proposal aligns strongly with the FY 2024 PRMRP strategic goals.

Hypotheses/Objectives: We hypothesize that ME/CFS patients exhibit altered DNA methylation compared to HC, which contributes to functional alterations in cellular and physical activity. We further hypothesize that the altered DNA methylation patterns of patients can be measured in their plasma cfDNA, which can be used as a molecular diagnostic tool for ME/CFS.

Specific Aims: In Specific Aim 1, we will isolate cfDNA from the plasma of ME/CFS patients and HC, perform WGBS and analyze data to screen for genes that are either hyper- or hypo-methylated in ME/CFS compared to HC, to carry out laboratory validation of top genes using direct bisulfite sequencing. In Specific Aim 2, we will directly use patients' plasma to carry out QMSP to develop a gene panel as biomarkers, using plasma cfDNA and PBMCs to validate the expression status of candidate genes to determine if DNA methylation of genes correlates with their expression, and carry out pathway and gene network analyses.

Study Design: We propose to use altered DNA methylation patterns to develop a diagnostic tool for ME/CFS. We will carry out WGBS on cfDNA from plasma of ME/CFS patients (n=30) and HC (n=30), validate the results using direct bisulfite sequencing and Quantitative Methylation Specific PCR (qMSP) using patient plasma, and PBMCs.

Innovation: This study will utilize WGBS for the first time in ME/CFS to map the methylation status of >28 million CpG sitea in the epigenome of ME/CFS patients compared to HC. We propose to develop top genes into a panel of biomarkers after validating the genes through direct bisulfite sequencing and qMSP using patients' plasma to examine a gene panel that could be used as disease biomarkers in ME/CFS patients. Our experimental approaches including WGBS, direct bisulfite sequencing and qMSP, using cfDNA as study model in ME/CFS for the first time. Thus, this study will be a pioneering and novel approach to screening for DNA methylation-mediated dysregulation in ME/CFS to utilize for developing biomarkers.

Impact: ME/CFS at present lacks efficient biomarkers for disease diagnosis. This study will enable us to develop a panel of biomarkers which will be highly impactful to the ME/CFS disease diagnosis, clinical testing, and decision making.

Relevance to military health: ME/CFS is a major clinical problem in veterans. There is a dire need for effective molecular biomarkers that could be used for patients' prognosis and diagnosis. In addition, the study involves the use of plasma samples from the veterans helping us to directly correlate the findings with the military health. Thus, this proposal aims at developing biomarkers for ME/CFS, addressing the present need of military health and in helping development of future therapeutic strategies.

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Identifying epigenetic determinants of ME/CFS using plasma cell-free DNA

Types of data produced

The types of data, software, curriculum materials, and other materials to be produced in the course of the project that are publicly releasable.

sequencing output from Whole Genome Bisulfite Sequencing

Data and metadata standards

The standards to be used for data and metadata format and content.

The data will be available in csv or txt file format in GEO database.

Conditions for access and sharing

Conditions for access and sharing including provisions for appropriate protection of privacy, confidentiality, security, intellectual property, or other rights or requirements.

The data can be accessed through Gene Expression Omnibus (GEO) database after the data has been deposited in GEO. The data will be deposited in GEO after the manuscript has been published/submitted from the study.

Conditions and provisions for reuse, redistribution, and derivatives

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Conditions and provisions for reuse, redistribution, and the creation of derivative works.

After the data has been deposted in GEO for public access, there is no general consition to reuse or redistribution. The data becomes public.

Plans for archiving and preservation

Plans for archiving datasets, or data samples, and other digitally formatted scientific data, and for preservation of access thereto. Explicitly describe how the data that underlies scientific publications will be available for discovery, retrieval, and analysis. In accordance with OSTP Memorandum, digitally formatted scientific data resulting from unclassified, publicly releasable research supported wholly or in part by DoD funding should be stored and publicly accessible to search, retrieve, and analyze to the extent feasible and consistent with applicable law and policy; agency mission; resource constraints; and U.S. national, homeland, and economic security.

The data generated from the Whole Genome Bisulfite sequencing will be initially processed, the data will be deposited into Gene Expression Omnibus, which will be publicly accessible. Similarly, the research outcome based on the data will be published in scientific peer-reviewed journal, which will also be publicly accessible.

Justification for the restriction of data

If, for legitimate reasons, the data cannot be preserved and made available for public access, the plan will include a justification citing such reasons.

The data will be made publicly accessible and there will be no restriction of the data to the public.
