ME-CFS26-001 - Uncovering the Genetic Contribution of Human Endogenous Retroviruses to ME/CFS

Abstract

Human endogenous retroviruses (HERVs) constitute a substantial and biologically active fraction of the human genome, yet they are largely excluded from human genetic studies of complex disease. In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), previous research has reported altered HERV expression, but it remains unclear whether these changes reflect secondary regulatory activation or underlying genetic variation at HERV loci.

The aim of this fellowship is to investigate the contribution of HERVs to the genetic architecture of ME/CFS by integrating population-scale human genetics with HERV-specific analytical approaches. Two complementary strategies will be implemented in parallel. First, non-reference HERV insertions will be identified from short-read sequencing data using specialized insertion calling algorithms to detect loci uniquely present or enriched in ME/CFS patients. Second, reference-based analyses will leverage cohort-level variant data to perform burden style testing at annotated HERV loci, identifying loci with altered mutational burden in cases compared to controls.

Discovered HERV loci will then be functionally interpreted by integrating regulatory and transcriptomic data. This includes assessing overlap with functional genomic annotations, enrichment for cis-expression quantitative trait loci (eQTLs), and overlap with loci previously shown to be transcriptionally active in ME/CFS cohorts. Permutation-based approaches will be used throughout to assess regulatory enrichment and tissue specificity under well-defined, locus-matched background models.

By systematically integrating HERV loci into population-scale genetic analyses, this project addresses a critical gap in current ME/CFS research. The results will advance understanding of how repetitive and regulatory genomic elements contribute to disease susceptibility and heterogeneity, with broader implications for post-viral and immune-mediated conditions.

Scientific disciplines:
Population genetics (60%) | Molecular biology (25%) | Bioinformatics (15%)

Keywords:
Human endogenous retroviruses (HERVs)ME/CFSHuman GeneticsPopulation GenomicsRare Variant Burden TestingInsertion PolymorphismsGene RegulationBioinformatics

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Further links to the persons involved and to the project can be found under
https://wwtf.at/funding/programmes/ei/ME-CFS26-001/