LITERATURE REVIEW | ME/CFS

Initial findings from the DecodeME genome-wide association study of myalgic encephalomyelitis/chronic fatigue syndrome

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DecodeME collaboration 2025 'Initial findings from the DecodeME genome-wide association study of myalgic encephalomyelitis/chronic fatigue syndrome'.
https://www.research.ed.ac.uk/en/publications/initial-findings-from-the-decodeme-genome-wide-association-study-

STUDY DESIGN AND SCOPE

The DecodeME study conducted the largest genome-wide association study of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), comparing DNA from 15,579 UK patients with ME/CFS against 259,909 healthy controls. All participants were of European ancestry, and ME/CFS cases were strictly defined using Canadian Consensus and/or Institute of Medicine criteria requiring post-exertional malaise and professional diagnosis.

MAJOR DISCOVERIES

The study identified eight genetic regions significantly associated with ME/CFS risk. These genetic variants contribute approximately 9.5% to the inherited risk of developing the condition (SNP-based heritability). Three of these regions contain genes that normally help the body respond to viral and bacterial infections (BTN2A2, OLFM4, RABGAP1L), while another region contains a gene (CA10) involved in pain processing.

CLINICAL SIGNIFICANCE

The genetic findings provide the first robust scientific evidence that ME/CFS has distinct biological underpinnings separate from psychiatric conditions. The study found no evidence that ME/CFS genetic signals share common causal variants with depression or anxiety, supporting ME/CFS as a distinct condition. The ME/CFS association near CA10 showed significant colocalization with multisite chronic pain associations.

BIOLOGICAL INSIGHTS

The identified genes suggest ME/CFS involves disrupted immune responses to infections and altered neurological processes. MAGMA analysis showed statistically significant enrichment of ME/CFS-related genes in 13 brain tissues. The OLFM4 genetic association was notably stronger in cases reporting infection at disease onset compared to those without reported infection onset.

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STUDY LIMITATIONS AND REPLICATION

Replication attempts in external cohorts showed limited success. In an analysis of 15,251 cases from seven national biobanks, no associations replicated after correction for multiple testing. However, in a more narrowly defined replication cohort of 13,767 cases requiring post-exertional malaise, four of the DecodeME loci showed association at $p < 0.05$ without multiple testing correction.

LAY SUMMARY

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a common, disabling illness. It affects more females than males, and in most cases, starts after an infection. Little is known about the biological mechanisms that cause ME/CFS, despite many attempts to uncover them, and it has no effective treatments. To understand ME/CFS better, our study, DecodeME, compared the DNA of 15,579 people with ME/CFS with the DNA of 259,909 people without ME/CFS, all of European descent. DNA is a molecule that makes up our genes. Our genes make many different molecules called proteins, each of which does very specific things in the body. Finding variations in genes that differ between people with or without a disease can therefore point to what causes it. We found that people with ME/CFS are more likely to carry certain DNA differences in eight regions of their genome, and so these variants tell us about possible biological causes of ME/CFS. However, as these differences are also often found in people without ME/CFS they cannot cleanly separate who is at risk and who is not, and therefore do not provide a definitive test. Most of these regions contain several genes. Our methods did not allow us to conclusively locate the ones most relevant to ME/CFS in each region, but public data allowed us to pick out the most likely ones. Three of the most likely genes produce proteins that respond to an infection. Another likely gene is related to chronic pain. None are related to depression or anxiety. We found nothing to explain why more females than males get ME/CFS. Overall, DecodeME shows that ME/CFS is partly caused by genes related to the immune and nervous systems.

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