Patients, scientists and advocates celebrate £3.2m funding for DecodeME, the largest ever ME/CFS DNA study

Funding for the world's largest genetic study into myalgic encephalomyelitis (ME), led by a partnership of patients and scientists, has been announced today.

Despite its high cost to patients, the economy, the NHS and society, very little is known about the causes of ME, also diagnosed as chronic fatigue syndrome (CFS, or ME/CFS), including how to treat it effectively.

Now, thanks to £3.2 million funding, awarded jointly by the Medical Research Council and National Institute for Health Research, work can begin on DecodeME, the ME/CFS DNA study that hopes to reveal the tiny differences in a person's DNA that may affect their risk of developing ME/CFS, and the underlying causes of the condition.

DecodeME will look at samples from 20,000 people with ME/CFS, in the hope that the knowledge discovered will aid development of diagnostic tests and targeted treatments.

ME/CFS affects an estimated 250,000 people in the UK, of all ages, and from all social and economic backgrounds. Post-exertional malaise, an adverse reaction to levels of exertion that many might consider trivial, is often considered to be the defining symptom - this can leave patients suffering from symptoms including extreme levels of fatigue, pain, inability to process information, and light and noise sensitivities. One in four people with ME/CFS are so severely affected they are house- and frequently bed-bound.

Andy Devereux-Cooke, one of the patients leading DecodeME, says: "As someone living with ME/CFS, I'm well aware that the patient community has waited a long time for a study such as this one that has such a strong, genuine element of patient involvement. All of us involved with this research project hope that it can start to address the totally unwarranted stigma and lack of understanding that so many patients with ME/CFS face on a daily basis."

Partnering with the MRC Human Genetics Unit at the University of Edinburgh and the London School of Hygiene and Tropical Medicine, it is being led by the ME/CFS Biomedical Partnership. This collaboration of researchers, people with ME/CFS, carers and advocates has grown out of the UK CFS/ME Research Collaborative (CMRC), established in 2013 by Prof Stephen Holgate, MRC Clinical Professor of Immunopharmacology at the University of Southampton.

Principal Investigator Prof Chris Ponting, MRC Human Genetics Unit, University of Edinburgh, says: "Our focus will be on DNA differences that increase a person's risk of becoming ill with ME/CFS. We chose to study DNA because significant differences between people with, and without, ME/CFS must reflect a biological cause of the illness. It is our hope that this study will transform ME/CFS research by injecting much-needed robust evidence into the field."

People with ME/CFS across the UK will be asked to volunteer to take part in DecodeME, which they can do from home, confirming they meet the selection criteria via a patient

questionnaire already being used by the CureME Biobank. Participants will be mailed a collection kit and asked to send back a saliva or "spit-and-post" sample. These will be compared with samples from healthy controls.

Sonya Chowdhury, Chief Executive, Action for M.E., and Chair of the study Management Group, says: "Simply put, we cannot do this without the determination and support of people with ME/CFS. Recruiting the 20,000 people we need is challenging – but absolutely achievable, by working in partnership with the CureME Biobank, charities, patient advocates, local support groups and others. People with ME/CFS can register their interest right now on the DecodeME website."

The samples will enable the Partnership to undertake the world's largest genome-wide association study (GWAS) of ME/CFS. Such studies have already helped to uncover the biological roots of many other complex diseases, including the identity of genes involved in Type II Diabetes, and the microglia (immune cells of the brain) that play a key role in Alzheimer's Disease.

Co-Principal Investigator Dr Luis Nacul, CureME Biobank, London School of Hygiene and Tropical Medicine, says: "Unlocking the genetic susceptibility to ME/CFS is a key part of understanding what causes ME/CFS and the disease mechanisms involved. This, in conjunction with other biomedical research into ME/CFS, should finally pave the way to better diagnosis and the development of specific treatments for this debilitating disease."

Professor Fiona Watt, Executive Chair of the Medical Research Council, which is helping to fund DecodeME, said: "This project is very significant in its scale and ambitions. It is one of the biggest studies into potential genetic connections to ME/CFS and I would like to congratulate Prof Chris Ponting and his colleagues on this award. It signals the shared commitment of funders, researchers and patients to work together to gain new insights into ME/CFS."

Dr Louise Wood, joint head of the National Institute for Health Research, said: "I am pleased to see the research teams in Edinburgh and the London School of Hygiene & Tropical Medicine, and patient groups, come together to take forward this important project which seeks to shine a light on the causes of ME/CFS for the benefit of people living with this debilitating condition. Patient involvement – one of NIHR's key values – has been embedded throughout, bringing huge relevance and value to the project."

The study is scheduled to begin in September, with recruitment of participants from March 2021. Anyone with ME/CFS aged 16 years or over who wants to take part in the DecodeME study can register their interest now www.decodeme.org.uk

ENDS

For more information, to request an interview with any member of the Partnership or to speak to someone with ME/CFS, please contact Clare Ogden, Head of Communications and Engagement, Action for M.E. Tel: 07496 199474. Email: clare@actionforme.org.uk

NOTES TO EDITORS

For more information about the study, please visit www.decodeme.org.uk (NB. Website will go live 00.01 Tuesday 23 June) or follow DecodeME on Facebook, Twitter, Instagram and LinkedIn @decodeMEstudy (formerly @mebiomed, it will be updated first thing on Tuesday morning).

The ME/CFS Biomedical Partnership study is funded by the Medical Research Council (https://mrc.ukri.org) and the National Institute for Health Research (https://www.nihr.ac.uk). The total award amount is £3,191,305.

ME/CFS is a chronic and fluctuating condition that may affect many body systems. People with ME/CFS experience severe, persistent fatigue associated with post-exertional malaise. Few recover, most remain ill for many years. Risk for ME/CFS is known, in part, to be inherited.

Biomolecular research into the causes of ME/CFS has long suffered from a replication crisis caused by most studies being considerably underpowered (ie. not large enough). Studies also often suffer from ill-defined disease criteria, cohort heterogeneity and failure to distinguish aetiology from symptomology.

A genome-wide association study (GWAS) is a very large genetic study that, by probing small DNA differences among people, can help to pinpoint the genetic causes of disease and guide drug development. This design has previously been helpful in identifying genes together with molecular and cellular pathways that contribute to disease risk.

To work well, this study needs to recruit around 20,000 patients whose DNA will be compared with that of a similar number of non-ME/CFS matched controls. These would be people from a similar population who do not have ME/CFS, such as people drawn from the UK Biobank (https://www.ukbiobank.ac.uk).

A GWAS has the major advantage that its results indicate root causes of illness, because DNA doesn't change with ME onset, so GWAS findings reflect causes rather than effects of illness. With most other approaches, it is not usually possible to know if findings indicate the effects of illness, or the cause. For example, people who are unable to exercise are likely to show molecular changes that are solely due to being sedentary, rather than highlighting the root causes of their disease.

The potential of GWAS to guide drug development for many illnesses was underlined by a recent study (*Cardon LR, Harris T. Precision medicine, genomics and drug discovery. Hum Mol Genet. 2016;25(R2):R166-R172. doi:10.1093/hmg/ddw246*). Its authors concluded from their analysis that using GWAS to guide the choice of which candidate drugs to develop could double the success rate for finding treatments that make it into the clinic.

We anticipate that pharmaceutical companies will begin to take an active interest in utilising the genetic information to help in the development of diagnostic tests, treatment targets and clinical interventions for ME/CFS, in response to research built on the firm foundation provided by robust GWAS findings.

Ultimately this study could improve many individuals' quality-of-life and health, and contribute to reducing the economic cost of ME/CFS to the UK, which in 2014-15 stood at £3.3 billion/year (https://www.theoptimumhealthclinic.com/wp-content/uploads/2017/09/Counting-the-Cost.pdf).

The ME/CFS Biomedical Partnership team is led by:

- Principal Investigator – Prof Chris Ponting, Chair of Medical Bioinformatics, University of Edinburgh
- Co-Principal Investigator – Dr Luis Nacul, CureME Biobank, London School of Hygiene
- and Tropical Medicine
- Patient and Public Involvement (PPI) Steering Group Chair and Management Group Chair - Sonya Chowdhury, Chief Executive, Action for M.E. (founding charity member of the UK CFS/ME Research Collaborative, or CMRC)
- Andy Devereux-Cooke, on behalf of the CureME Biobank Steering Group and as part of the PPI Steering Group.

Prof Chris Ponting (https://www.ed.ac.uk/profile/chris-ponting) is a human genetics and genomics researcher whose expertise traces back to the human and mouse genome sequencing projects to whose publications he contributed scientific leadership. His current research interests include revealing molecular mechanisms causing complex disease risk, the single cell biology of the thymus, and whether T-cell receptor signatures can distinguish ME/CFS cases from controls (a study that uses UK ME/CFS Biobank samples). He has served as Deputy Chair of the CMRC since 2018.

The CMRC (https://www.actionforme.org.uk/CMRC), chaired by Prof Stephen Holgate, was established in 2013, with support from the Action for M.E., the ME Assocation, the MRC and other stakeholders, to enhance ME/CFS research by promoting interdisciplinary collaboration in partnership with patients and carers. In January 2018, its five-year review point, the CMRC recognised that, despite some successes, there had been little change to the research landscape for people with ME/CFS. This was also recognised at governmental level. Prof Dame Sally Davies (then Chief Medical Officer for England) and Prof Chris Whitty (joint head of the NIHR) discussed with the CMRC how the then Department of Health and the NIHR could catalyse a step-change in impact and quality of ME/CFS research. The CMRC's conclusion was to lay the foundation of a UK ME/CFS research platform utilised for discovery multi-modality 'omics, identification of causal pathways, delivery of much needed diagnostic tests for disease stratification, and an opening up of experimental medicine and clinical trial opportunities. In 2019, a joint MRC/NIHR workshop with CMRC, CureME biobank, people with ME/CFS and carers agreed the ME/CFS Biomedical Partnership's scientific aims and funding envelope.

Dr Luis Nacul is a clinical ME/CFS specialist and an Associate Professor in Epidemiology and Public Health who is leading ME/CFS research internationally with partners in America, Europe and Australia. He was the Principal Investigator for the feasibility study on a disease-specific Biobank for the study of ME/CFS and the London lead for the CFS/ME Observatory project. He is Director of the CureME Research Programme (https://cureme.lshtm.ac.uk/the-uk-mecfs-biobank) at London School of Hygiene and

Tropical Medicine, and Medical Director of the Complex Chronic Diseases Program in British Columbia Women's Hospital, Canada (80% time commitment). In addition to serving as co-PI for Canadian Research Collaborative in ME, he is the PI of the UK ME/CFS Biobank (UKMEB).

Sonya Chowdhury has been Chief Executive of UK charity Action for ME (https://www.actionforme.org.uk) for seven years and – in having a teenage son with ME – brings both personal and professional insight to the project. Sonya has extensive leadership experience and has forged national and international collaborations and partnerships with children and adults with ME and other key stakeholders.

Andy Devereux-Cooke has had ME/CFS for more than 35 years. He is a co-founder and committee member of the online forum Science for ME (https://www.s4me.info) and is a patient representative on the CureME Steering Committee. He will inform this project with both his personal experience and his awareness of the issues that are important for the patient community.