The ME/CFS Biomedical Partnership: Genetics and Biomarkers

Genome-wide association study: questions & answers

What is the ME/CFS Biomedical Partnership?

ME/CFS Biomedical Partnership: Genetics and Biomarkers is the working title for a partnership of researchers, including Professor Chris Ponting (pictured left) and the CureME UK ME/CFS Biobank (UKMEB) team headed up by Dr Luis Nacul (pictured right), and ME/CFS patients, carers and public. Early in 2020, the partnership will make a grant application to the Medical Research Council (MRC) and the National Institute for Health Research (NIHR) for a very large genetic study, a genome-wide association study, and a major expansion of the UKMEB.

Below we provide questions put forward by members of the Science for ME online forum. Our answers were initially drafted by one of us (CPP) and Simon McGrath, a frequent blogger on ME/CFS biomedical research. Changes were then suggested by others in the Partnership and community. Issues raised often provoked further questions which we then also tried to answer. All contributions have hugely improved this set of Q&A and will improve the project itself, should it be funded.
We think of this as a *living document* so hope to update it further in the future. One update we will do as soon as possible is to provide detail on the UK ME/CFS Biobank expansion.

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Summary

- The Partnership will apply for funding for a large genetics study as well as an expansion of the UK/ME CFS Biobank
- If funded, the genetics study will require saliva samples from 20,000 patients.
- The study will look for the potential genetic cause(s) of ME/CFS.
- Submitting a sample will be made as easy as possible in order to enable as many patients as possible to take part.
- Patients, and their representatives, will form an important part of the Partnership.

1. What is a genome-wide association study?

A genome-wide association study (GWAS) is a very large genetic study that seeks to uncover some of the biological roots of ME/CFS. By probing small DNA differences among people, a GWAS can help to pinpoint the genetic causes of disease and then can help to guide drug development. This design has previously proved helpful in identifying genes together with molecular and cellular pathways that contribute to disease risk. *Read more about the* science of GWAS.

To work well, the study needs to recruit around 20,000 patients whose DNA will be compared with that of similar numbers of non-ME/CFS matched controls (i.e. people from a similar population but who do not have ME/CFS),.

2. How will the study ensure that all participants recruited to the trial really do have ME/CFS?

We take participant selection very seriously. We will be using the CureME patient questionnaire that has been in use for the UK ME/CFS Biobank for several years. This is additional to your report that you've been diagnosed with ME or CFS by a clinician.

GWAS need to be very large to generate robust results and it wouldn't be economically feasible to clinically assess every patient independently. However, as part of the study, some patients will have

an assessment by a clinician with knowledge of ME/CFS to confirm the diagnosis is accurate. We anticipate this work will find a high proportion of patients who have been accurately diagnosed, and a GWAS does not need 100% diagnostic accuracy to produce valid results.

3. What case definitions will be used (specifically, what about the Oxford and NICE criteria)?

CureME will apply its diagnostic algorithm (a very specific set of rules) to assess people according to well accepted diagnostic criteria: the Institute of Medicine 2015 or the 2003 Canadian Consensus or Fukuda, but not Oxford or NICE, criteria. Post-exertional malaise (PEM) will be a mandatory symptom. This is because patients, patients' organisations and ME/CFS biomedical researchers all regard it as a defining symptom of the disease. Using these definitions help to ensure that findings are compatible with those used in biomedical research around the world.

4. How can people with ME/CFS take part?

We are working very hard to make taking part as easy as possible. Our plans are for just two steps: First, potential participants will register online or by returning a paper form sent to the CureME team. Second, accepted participants will be asked to post a saliva sample to the project using a collection kit which they will receive by mail (a "spit-and-post" sample). Some participants, e.g. those who are already part of other studies or the UKMEB and who have previously consented, may be contacted directly by the researchers.

The GWAS is open to anyone who already has a diagnosis of ME or CFS from a clinician and who also meets the CureME research diagnostic criteria as assessed by questionnaire and in some cases complemented by a clinical assessment by the CureME clinical team. People who meet these criteria will receive a sample collection kit through the post so that they can return a saliva sample using the freepost envelope provided.

When we receive it back, we will extract DNA and then look at nearly a million "variants", places in the human genome where the DNA commonly differs from person to person. These DNA variants make people different from one another, and in some cases make people more or less likely to develop some diseases. They also play a role in determining many things about us, such as our height, weight and intelligence.

All participants must meet the recruitment criteria, but not meeting the criteria does not mean that someone does not have ME/CFS.

5. Can those who are severely affected take part?

We have chosen online recruitment and the "spit-and-post" design. This makes it possible for people who are severely affected with ME/CFS to join the study. It may also be possible for family, friends and carers to assist in completing the questionnaire and sending back the saliva sample.

6. To maximise recruitment, will the online questionnaire be short? And will there be a paper questionnaire alternative, for those who struggle to use the Internet because of their illness or another reason?

We understand that questionnaires can be very tiring for people with ME/CFS, particularly for those who are severely affected. The questionnaire will be designed to balance the need to capture a person's relevant information with the need for brevity.. We plan to offer a paper questionnaire as well as the online version. As these are completed at home, participants may complete the questionnaire in more than one go.

7. How will we use the survey, biological and genetic information that people provide?

Our goal is to identify causes of ME/CFS. For this we will first isolate and analyse your DNA from the saliva sample. We will then look at around a million common variants in DNA and see if any of the

variants are more or less common in patients than seen in control individuals. Survey data such as age, type of onset and symptoms will be used to gain a better understanding of your background and illness and we will link this survey data to your genetic data.

We may also ask people if they are willing to provide us access to their electronic health record, with personal clinical information kept by their GPs. This would help us to get a more detailed understanding of your illness, progression and symptoms, but would be entirely optional and would not affect eligibility for the study.

8. How will samples and data of participants be kept secure and private?

We take sample and data security, and your privacy, very seriously. All samples and data will be kept secure according to the UK's and international highest standards overseen by ethical review. All institutions contributing to this project have adopted these standards and use them routinely, and comply with the Human Tissue Act 2004 and all other relevant regulations and legislation, including the General Data Protection Regulation (GDPR). The UKMEB has extensive experience in doing research in ME/CFS including the international distribution of samples to researchers worldwide, always ensuring the highest level of privacy from participants and full compliance with ethical standards and legislation.

9. Will the target number of cases be big enough to generate meaningful findings, and to detect any subgroups?

Until the first GWAS study for an illness is done it is just not possible to know how meaningful its findings will be. However, we've chosen to study 20,000 people with ME/CFS because other projects of this size commonly have found around five causal links between DNA and disease diagnosis.
ME/CFS could have many independent genetic causes and a study of this size will have a chance of revealing part of this potential spectrum of genetic causes.

10. How will the study ensure the support of the patient community?

The study will only reach its participant target with the active support of people who have the disease. The Management Group of this study will include both researchers and public and patient/carer representatives. In addition, both the Patient Advisory Group of the CMRC and the Steering Committee of the CureME Biobank which includes patients and charities will be involved in all aspects of the project. The project will always adhere to the CMRC's values, which include the following:

- We are a collaborative community inviting all stakeholders to join our programmes and shape our activity.
- We support and expect the highest quality research.
- We encourage insightful questions and open and informed debate; we applaud and listen to those who have questions about research.

We are working with a representative from the CureME Biobank Patient Group, Andy Devereux-Cooke who is also a co-founder of Science for ME forum, and one from the CMRC, Sonya Chowdhury, CEO of Action for M.E., to help set up a Patient and Public Involvement (PPI) Steering Group. Additional members will include:

- Countess of Mar, on behalf of Forward M.E. and the patients/carers the member organisations represent
- CMRC Patient Advisory Group representative
- Charles Shepherd, on behalf of ME Association and as a Patient Charity representative on CMRC from its inception.

The Group met for the first time on 4 November 2019 and agreed how it will work together. It will ensure that its terms of reference are made available, alongside other key documents and minutes from meetings. There will be other mechanisms for people not represented through the organisations

represented on the Steering Group, to engage with the project; more information will be available as soon as possible on this.

Patients will always be at the heart of the study.

11. How will the study manage to recruit so many patients?

Recruiting so many people with ME/CFS will be a huge challenge, particularly as it is not as common as, for example, diabetes (around one in 250 people have ME/CFS, compared to 1 in every 16 for diabetes). It is also the case that many people do not have a clinical diagnosis. So it is clear that the support of people with ME/CFS and their carers, as well as the different ME/CFS charities, will be critical to the successful recruitment of 20,000 with ME/CFS.

With guidance from patients, carers and professionals, we will put together a recruitment campaign. The proposal is being backed by all the charities within Forward ME: the ME Association, ME Research UK, Action for M.E., #MEAction, the ME Trust, the 25% M.E. Group, the Young ME Sufferers Trust, reMEmber, Blue Ribbon for Awareness of ME and the Neurological Alliance.

12. Will this be an international study, recruiting patients in multiple countries, and collaborating with researchers beyond the UK?

We are considering recruiting patients diagnosed with ME/CFS who live outside the UK. This would need to meet the appropriate high ethical standards to protect the privacy of individuals from other countries in the same way as people who are in the UK.

13. Will the study recruit from fatigue clinics and might that affect diagnostic accuracy?

We will be looking to recruit people with a clinical diagnosis of ME/CFS (and who pass the Cure ME diagnostic algorithm). These may include people attending fatigue clinics although many attendees of these clinics will not have ME/CFS. We anticipate that the bulk of participants will be recruited to the study through social and traditional media, and through our contacts with charities.

14. Can you give examples of how genome-wide association studies have helped progress understanding or treatment of other diseases?

Findings from such studies have helped to:

- establish the identity of numerous genes involved in Type II diabetes, such as those affecting the action of insulin on fat cells and liver cells. These studies have also helped to identify an unsuspected role in Type II diabetes for a protein that transports zinc into cells, and scientists are developing drugs that target this protein.
- reveal that microglia, the immune cells of the brain, play a key role in Alzheimer's disease.
- demonstrate that thermogenesis, where "brown fat" cells burn off fat to produce heat, is an important pathway impacting on obesity.
- show that high levels of "good" HDL-cholesterol is simply associated with lower levels of heart disease — but is not actually protective. This explains why the pharmaceutical industry's $5 billion investment in drugs that increase HDL-cholesterol came to nothing. Instead, GWAS helped to show that a different type of fat, triglycerides, does increase the risk of heart disease.
- establish that many different diseases often share some common biological mechanisms. An immune-regulating molecule called IL-23 plays a significant role in numerous autoimmune diseases. As a result of this insight, existing drugs that are used to inhibit the IL-23 pathway in other diseases have become a mainstay treatment for several autoimmune conditions, including psoriasis and ankylosing spondylitis.

15. Why this particular approach over others?

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.

GWAS have been successfully applied to many different diseases (asthma, schizophrenia, diabetes, pulmonary disease etc – see a comprehensive list here) and traits. We believe that it is time that ME/CFS science took full advantage of this cutting-edge genetics approach which is entirely complementary to approaches taken by other ME/CFS researchers.

16. Why don't researchers just do the analysis on all the existing ME/CFS Biobank samples to see what it reveals first?

Existing samples from UK ME/CFS Biobank will be used. However, we need a very large number of people for a GWAS study, typically at least 10,000–20,000 patients. This will require a significant expansion of the UKMEB, and collaboration with the NIHR Biosample Centre in Milton Keynes.

17. Wouldn't it be better to back research to find a reliable biomarker first, to ensure participants in this kind of study actually have ME/CFS?

As yet, there is no such biomarker and despite some promising research, there is still no test that can reliably separate people with ME/CFS from people with other, similar diseases. We know that others around the world (e.g. Stanford, Harvard and Uppsala) are actively pursuing biomarker research, and we hope they are successful. But there is no guarantee of success and the timescale to development is uncertain. So, it is our view that we should press ahead with our complementary approach.

18. Will the study have a serious, scientific-sounding name? Acronyms for medical studies can sometimes sound forced and trivialising.

The working title for this project is *ME/CFS Biomedical Partnership: Genetics and Biomarkers*. We have not reduced this to an acronym.

The study will need a short and memorable name to use in promotion which means something to the majority of people with ME, who may not have the energy to follow the research. We will consult with patients before finalising the name which will be serious, will not trivialise the illness and will not be an acronym.

19. Will the project be requesting a budget to fund recruitment activity?

Yes, Patient and Public Involvement (PPI) will be essential to the scientific success of this project. We plan to request funding from the MRC and NIHR for the recruitment of participants, data and sample collection and analysis of results.

20. Will the study team provide supporting materials to patients, such as posters for GP surgeries?

The aim is to provide patients with good materials to support recruitment. We will engage with people with ME/CFS at every stage of the process on what is appropriate, but materials might include videos for social media, posters for GP surgeries and template letters for writing to local papers.

21. What happens if, after all this effort and money, the study finds nothing? Will the MRC say, "That's it, we're not funding any more research into ME/CFS"?

As with all research studies, there is no guarantee that this GWAS will make significant findings. However, the GWAS is only one aspect of this project, the other being the expansion of the UK ME/CFS Biobank so that it will contain samples from about 1,000 people with ME/CFS. Funders would support

expansion of the Biobank in the expectation that it will continue to facilitate numerous and diverse studies into the biomedical causes of ME/CFS.

22. Will psychosocial researchers be involved?

No — the lead investigators are a specialist in human genetics (Chris Ponting, Professor for Medical Bioinformatics at the MRC Human Genetics Unit), and a clinician (Dr Luis Nacul, who heads up the CureME team and the UK ME/CFS Biobank). All researchers in this project are focused on biomedical research.

23. How long will the GWAS study take to complete?

In total, four years but we will release preliminary results as soon as we can, prior to publication. The sooner we can recruit participants, the sooner the results will be released.

24. How likely do you think it is that the MRC will fund the proposal?

In general, there is a 20% chance that any grant proposal is funded. Nevertheless, we believe that there is a good scientific and impactful argument for funding, and we will make this as strongly as we can.

25. Will participants have the chance to take part in future studies as well?

When people sign up to this study, we will ask them if they are willing to be contacted about taking part (directly, or by agreeing to share samples and data from this study) in new studies, either related to this one or unrelated. This will make it much easier for researchers to recruit participants for studies, speeding up the pace of research.

We'd like to thank everyone who asked questions about the GWAS idea on the Science for ME forum, as well as the many people with ME or their carers who made helpful suggestions and comments on the various drafts of the Q&A. They have helped to improve the Q&A and importantly to improve the project itself.