The UK MND Collections – DNA Samples

A biorepository of samples and clinical/epidemiology data from people living with Motor Neurone Disease

THE UK MND COLLECTIONS

MND Collections

- MND Collections DNA Bank
- MND Collections Cell lines
- MND Collections Epidemiology data

INTRODUCTION

Motor Neurone Disease (MND) is a fatal, rapidly progressing neurodegenerative disease that affects the brain and spinal cord. It kills a third of people within a year and more than half within two years of diagnosis. Six people are diagnosed every day and there is currently no cure and the only approved drug in the UK extends life by up to 3 months.

The UK MND Collections[1] evolved from the UK MND DNA Bank [2], which is an internationally recognised and unique resource set up in 2003 to assist researchers in finding the causes behind MND.

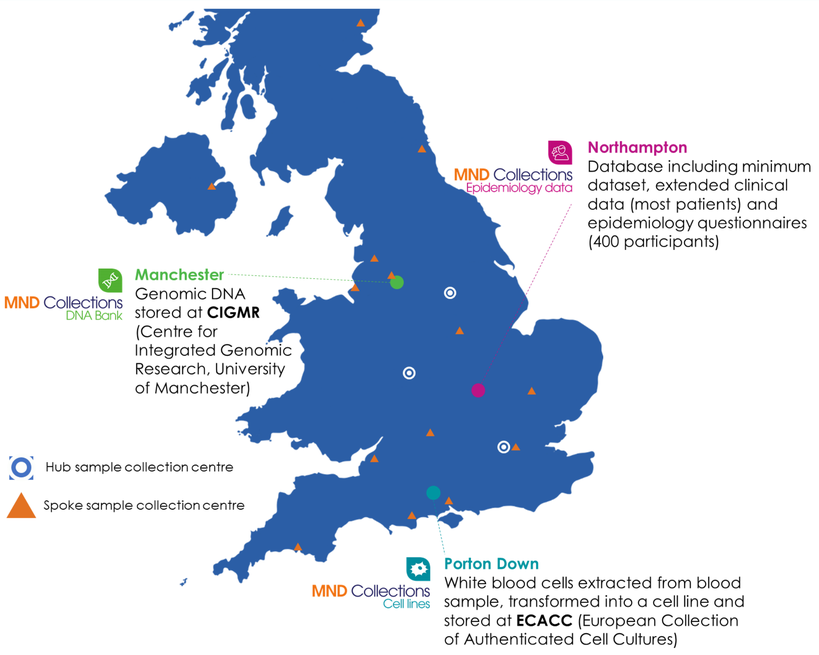
>3000 people living with MND/spouse controls provided blood samples (DNA was extracted using Nucleon BACC3 protocol), along with clinical/phenotypic data, between 2003 and 2012.

Lymphoblastoid cell lines (via Epstein Barr virus transformation) were also produced from the white blood cells of the majority of these samples.

An epidemiology survey was conducted on 200 participants and 200 separately matched controls. Data examples include: lifestyle, health, employment and environmental exposures.

Sample collection concluded and the resource became fully accessible in 2012 with >50 papers published to date and data/samples shared with over 20 countries across the world.

SAMPLES AND DATA



- All biological samples have a minimum dataset: age at sample taken, gender, affectation status, diagnostic certainty (El Escorial status) and age of onset (and survival years where available). Access to additional clinical[3] and epidemiological[4] data is via application.
- Epidemiology study – data collected by a self-report questionnaire, followed by a telephone interview with a research nurse.
- Samples/data are free to access for academic/not for profit organisations (a small admin and shipping charge from CIGMR and ECACC applies).
- Samples were anonymised and an ID code allocated (which is used in our database) on the patient notes (stored securely at Hub centres).
- CIGMR operates under ISO900:2000 standards. DNA normalised to stocks of 100ng/µg and stored at -80°C.
- ECACC operates under ISO 9001:2015 standards under HTA license 12114. Cell lines are split into a familial (inherited) range (searchable on the ECACC website)[5] and a sporadic (non-inherited) range. Multiple aliquots of each sample were produced. Master and working cell banks for the familial range were produced to prevent phenotypic drift. These have been used to create induced pluripotent stem cells (iPSCs) (Poster 2).

DATA ENRICHMENT AND DEVELOPMENT

- Original samples and data have been further added to by projects using Genome Wide Association Studies (GWAS), Whole Genome Sequencing (WGS), Exome Sequencing, methylation, SNPs and MicroRNA analysis.
- Samples can be used in research of related conditions, such as fronto-temporal dementia (FTD).
- Participant consent allowed for commercial use (unusual for MND samples), meaning international companies approach us for sample use.
- All data produced must be made available by the researcher on a publicly accessible database <6 months after publishing. Some types of data e.g. gene mutations present in our samples, are sent back to us for other researchers to access.

OBJECTIVES

- Governance - the MND Association acts as custodian for the Collections, access decisions are made by our Biomedical Research Advisory Panel (BRAP) and the principal investigators of the Collections, no researcher may attempt to contact any participant, full T&Cs available[6].
- We have a dedicated section of our website with details of samples/data and the application process, as well as an email address for enquiries (mndcollections@mndassociation.org).
- Sample/data access is achieved usually between 3 weeks and 3 months after the successful submission and approval of a completed application form[7].

RECENT SAMPLE USAGE

Year of application	Number of applications received	Number of applications approved	Number of samples or data accessed
2015	4	4	4057
2016	5	5	640
2017	3	3	1215
2018	4	4	201

CASE STUDY 1 - DNA Samples used in Project MinE

Professor Ammar Al-Chalabi, King's College London

INTRODUCTION:
Project MinE is an international genome sequencing consortium that started in 2013, in the Netherlands, and now includes a total of 20 participating countries.

OBJECTIVES:
- To map the full DNA profiles of at least 15,000 people with ALS and 7,500 control subjects, and to perform comparative analyses on the resulting data[8].
- To identify the last remaining major type of gene variation, namely rare or moderate frequency variants contributing to apparently sporadic ALS risk.

METHODS:
WGS, GWAS and methylation chip array.

RESULTS SO FAR:
- MND Collections has contributed over 1,800 samples (sporadic MND and controls), the largest contribution by any country outside of the Netherlands. All of these have undergone WGS and the methylation chip array is almost complete.
- Analysis of resulting data is ongoing (>10,000 samples have undergone WGS), with 6 working groups now set up, demonstrating cross-collaboration internationally, to focus on different analyses including epigenetics and phenotype/genotype associations.
- So far, at least 6 new genes have been found to be associated with MND.
- Many peer-reviewed papers already published[9], this increases every year.

FURTHER COLLABORATION:
- MND Collections was the second cohort outside of the Netherlands to join this initiative which helped give the project credibility to go global.
- Prof Al-Chalabi (the lead PI for the UK) shared his successful grant application, as a template, with many other countries to assist their funding applications.
- One of the working groups is focused on ethically optimising data sharing to accelerate drug discovery with commercial partners.
- Other countries are now sharing their WGS data (done separately) to enrich the data collected in Project MinE.
- New collaborations with Answer ALS, Target ALS and the New York Genome Center.
- Dutch government agreed to cover the huge cost for Project MinE to have dedicated space on SurfSara (national supercomputer).
- Data sharing is currently underway to enhance the ENCALS (European Network for the Cure of ALS) survival prediction model.
- New citizen science project underway (in testing phase) to allow mobile phones to analyse small sections of genetic data to contribute to data analysis computing power.
- Most of our samples have a matching cell line available (the only Project MinE country who can offer this), discoveries in the data can be modelled very closely/confirmed in the laboratory.

Project MinE Consortium members and patient ambassadors (27th International Symposium on ALS/MND, Dublin 2016)

IMPACT:
- Two papers about new risk variants [10,11] e-published the same day received a lot of media coverage both in the UK and internationally. Multiple interviews (including radio and television for BBC News, Channel 5 and The Guardian newspaper) were given by Prof Ammar Al-Chalabi and MND Association staff.
- As a direct result of Project MinE – Prof Al-Chalabi gained EU JPND funding for STRENGTH and BRAIN-MEND (both are multi-national and multi-million pound projects).
- A free tool to detect the C9orf72 repeat expansion from WGS data has been developed[12]. This was not previously possible and can be applied to other repeat expansions outside of MND.
- Knowledge gained from Project MinE resulted in post-hoc analysis of a previous 'failed' drug trial of Lithium, showing an affect on people with gene UNC13A mutations. New worldwide funding application for Phase 3 trials is underway with the MND Association contributing funding.

ENGAGEMENT AND RECOGNITION:
- MND Association staff are active in promoting Project MinE to the wider public. With lay articles appearing in our member and volunteer magazines (>15,000 people) as well as on our research blog, newsletters and general & research twitter accounts (>34,000 followers). Talks, aimed at people affected by MND, are regularly given at our regional conferences, branch/group meetings and major donor/legacy events.
- Research team staff also promote within the MND Association with posters at annual staff conference and on our intranet.
- Encourages further fundraising to contribute to Project MinE funding eg the MND Association was Credit Suisse charity partner 2017, Amsterdam and London City Swims, raising > £500,000 for Project MinE work.
- Large amount of promotion to 4,000 Credit Suisse staff through lunch & learn sessions and an end of year presentation.
- Prof Al-Chalabi received the Sheila Essey Award (American Academy of Neurology) in 2016.
- Researchers promote through twitter and YouTube as well as presenting at conferences.
- International Symposium on ALS/MND (the premier research conference on MND) last year attended by >1,200 delegates from 39 countries. Talks/posters are presented every year since the project began, the MND Collections are advertised in the abstract book. Project MinE satellite meeting for all involved researchers is held annually at the Symposium.

ACKNOWLEDGEMENTS AND REFERENCES

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1) https://www.mndassociation.org/research/for-researchers/resources-for-researchers/ukmndcollections/, 2) Smith et al. BMC Genetics Establishing the UK DNA Bank for motor neuron disease (MND) (2015) 16:84, 3) www.mndassociation.org/extdataset, 4) www.mndassociation.org/epidataset, 5) https://www.phe-culturecollections.org.uk/products/celllines/diseaseandnormalcohortcollections/search.jsp , 6) www.mndassociation.org/collectionsterms, 7) www.mndassociation.org/applicationdna, 8) https://www.projectmine.com/about/ 9) https://www.projectmine.com/research/publications 10) NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. Kenna KP, van Doormaal PT, Dekker AM, et al. Nat Genet. 2016 Sep;48(9):1037-42. doi: 10.1038/ng.3626. Epub 2016 Jul 25. 11) Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. van Rheenen W, Shatunov A, Dekker AM, et al. Nat Genet. 2016 Sep;48(9):1043-8. doi: 10.1038/ng.3622. Epub 2016 Jul 25. 12) Dolzhenko E, et al. Detection of long repeat expansions from PCR-free whole-genome sequence data. Genome Res. 2017 Nov;27(11):1895-1903