HUNTINGTON'S DISEASE NEWSLETTER 2023

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Welcome to our latest newsletter!

Welcome to our 2023 HD newsletter which we hope you will find of interest. It has been a busy year both in terms of research and our outpatient clinic work given the major stresses and strains on the NHS currently. In this respect, I am delighted to say that we have a new neurology consultant working in the clinic now – Dr Tom Stoker. Tom started in August of this year helping us with this clinic , so many of you will soon get to meet him. Tom was with us a few years ago doing research and we are so pleased that he has decided to come and work with us again. This should help us see people more quickly in the clinic as the numbers being referred to our service continue to increase, which is a good thing, but has made it tricky for us to see everyone in as timely fashion as we would like (p3)!

As part of improving our service we have for the last year or so also set up a new virtual meeting every few weeks between the clinic staff here at the Brain Repair Centre and Dawn and Rachel from the HDA (p4). This allows us to exchange notes on clients so as to try and ensure that the care and support we give to you, is better co-ordinated and communicated.

On the research front we have continued to make good progress both in terms of our own work as well as drug trials with companies. In this latter respect, Katie and her team have done sterling work looking at drugs that not only are being trialled to help with some of the clinical aspects of HD (e.g. SOMCT03) (p7) but ones that may slow it down. This includes a new trial using a similar approach to the one we did before with Roche around trying to silence the production of huntingtin protein using an ASO approach (p6).

In terms of our own work, Dimitri, Katie and Amy have been busy running the FELL-HD trial (p5). This trial is seeking to see whether we can use a drug, felodipine (a drug that is already in routine clinical practice for treating high blood pressure) to slow down HD by working to clear the protein from the cell more efficiently. So far the trial is going well and we hope to share the results of it next year.

Zanna and a new student, Natalia, continue to do exciting work on sleep in HD (p10 and 14). This builds on years of work by us showing that sleep does go wrong in HD, the question we are now asking is, what does this mean in terms of not only how you feel but what it does for the disease process? Namely, does bad sleep drive the disease process and if so can we treat it and thus slow down disease progression- a therapeutic area we would like to explore in the near future.

We also continue to be very interested in the types of thinking problems in HD and what this actually means for everyday life. Miriam has taken this on with her projects (p11/12) building on work done by Sarah Mason when she was full time with us. In addition, Amy is continuing to explore how some of the drugs we routinely use in the clinic affect thinking, which may have important implications for how we treat people with such agents (p8).

Finally we are always on the look out for better ways to measure how the disease is affecting individuals. We have done this with blood tests in the past including an ongoing study using a technique called SERS (which is led by Tagore who has come back to join us for a year, p15). We are also now looking at whether there are subtle changes in the eye that may track HD progression, which has been made possible by the independent funding of a new vision lab in the hospital (p13).

So thank you for all your continued support in our research and do continue to let us know how we can improve what we do.

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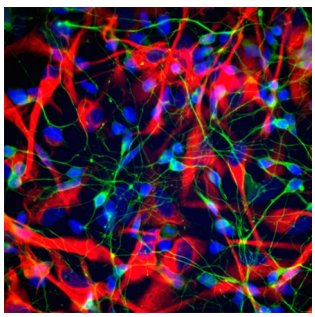

A mixed culture of human cells grown in a dish. Neurons are shown in green, the supporting astrocyte cells found in the brain, are labelled in red and the nuclei of all these cells are shown in blue.

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Huntington's Disease NHS Clinic

Clinic Contact Details

To reach us please leave a message on the HD clinic answer phone or email the clinic and we will get back to you.

HD clinic direct line: 01223 761863

HD clinic email: add-tr.hdclinic@nhs.net

Our clinics are running well with Mondays continuing to be phone and video calls and Wednesdays face to face appointments. Throughout 2022 we conducted 196 virtual appointments and 276 face to face appointments. Compared to the previous year our face to face appointments have almost doubled.

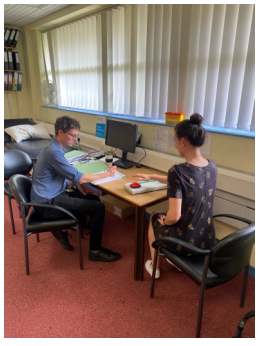
From mid-August we are delighted to be welcoming back Dr Tom Stoker who will be helping us with our Wednesday clinics along with Roger. As always we thank you for your patience and flexibility with us when it comes to booking your appointments and dealing with queries you may have.

Appointments

Our clinics do constantly remain fully booked, if you can not attend or need to rearrange please let us know as we currently have over a 4 month wait. HD clinic appointments are being arranged by the hospital. You will notice that:

Your appointment letters will come on Cambridge University Hospital NHS Foundation Trust headed paper

To re-arrange your appointment, you will need to ring the hospital number contained in the appointment letter.



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Huntington's Disease Association

Dawn Stilwell: Specialist HD Advisor (HDA)
Telephone: 01733 301036
Email: dawn.stilwell@hda.org.uk

Rachel Boothman: Specialist Advisor (HDA)
Telephone: 01536 211496
Email: rachel.boothman@hda.org.uk

Dawn started at the HDA in 2021 as a Specialist Huntington's Advisor covering Cambridgeshire, Norfolk, Suffolk and Essex. She brings many years of experience working for charities supporting people with disabilities and their families.

Alongside Dawn, Rachel also joined the HDA at the same time covering the areas of Hertfordshire, Bedfordshire and Buckinghamshire. Rachel is an Occupational Therapist and has worked in the NHS and/with the Motor Neurone Disease Association.

Rachel and Dawn both enjoy the challenges of supporting people and their families in managing and living with HD. Both of them link in with the HD clinic on a regular basis in order to support patients better and to discuss any additional support which may be needed within the community.

Our advisers are completing home visits and attending support groups. They can also support families by more remote methods such as telephone or video calls. They can also give you details about local branches and support groups or opportunities for peer support in your area. Please get in touch if you think either Dawn or Rachel can help you with your issues.

They hold regular events on many different aspects of Huntington's disease.

The Peterborough support group meets monthly, usually on the third Friday of the month, if you would like more information please contact Dawn via the contact details above.

They also have webinars and events running through the year, these can be found on their website (www.hda.org.uk/information-and-support/information-resources/events/)

If you would like to be kept up-to-date and hear about all future events please go to the HDA website and follow the 'keep in touch' link (https://www.hda.org.uk/get-involved/communication-consent) where you can sign up to email notifications from the HDA. They also advertise all of their events via social media.

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FELL-HD study

Funded by UK Dementia Research Institute



At the beginning of last summer we started our Fell-HD trial. This trial originated from work done in Cambridge by David Rubinsztein and his lab looking at removing the mutant huntingtin that carriers of the HD gene produce.

The main intervention is the administration of an oral medicine called Felodipine. This drug is already licensed for use in humans to lower blood pressure and in the preclinical experiments by David, it showed promising results in lowering the aggregates of Huntingtin protein in the cells. The benefit of using a drug that is already being used for another condition (so called drug repurposing) is that we have greater confidence that the drug can be used safely and have some idea of what, if any, side-effects to expect. However, because we are using Felodipine in a slightly different way to the way it was intended, we need to check that the drug can be tolerated by people with HD at the dose we need to use, while also exploring whether there is any suggestion of it slowing disease progression in HD.

This is mainly carried out by conducting a sub study called Fell-HD-s that allows us to study disease markers known to track disease progression and understand the impact felodipine might have on them. Everyone participating in the main study has kindly signed up for the sub study. Fell-HD and Fell-HD-s cumulatively include assessments such as brain MRIs, spinal fluid and blood collection along with various clinical tests, that in combination will allow us to explore whether there is any suggestion that this drug may be slowing down the disease.

The trial completed recruitment in February 2023 and is expected to conclude in April 2024!

If you would like to know more about this trial, please contact Dimitrios via email da539@cam.ac.uk or telephone 01223 767761

Participants will be having MRIs to look at any changes in the brain

FELL-HD

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Silencing the abnormal Huntington's gene

Funded by Roche Pharmaceuticals

Since 2016, we have been involved in trials to investigate the impact of silencing the abnormal HD gene product that was originally funded by IONIS and then by Roche pharmaceuticals. The agent, called an antisense oligonucleotide or ASO, has been designed to lower the level of Huntingtin in the brain by telling cells to delete the 'message molecule' that is being coded for by the Huntingtin gene. The American Pharmaceutical company IONIS began the trials back in 2016 with the initial results published in 2019. Roche then bought the license to the drug in 2018 and renamed the agent Tominersen.

The trials over the last 3 years have been called Gen Extend and Generation HD1. Gen Extend was an open label treatment trial, meaning all participants received active drug and this aimed to provide answers about the long term safety and tolerability of Tominersen. Generation HD1 was a double blind, placebo controlled trial, meaning the participants and trial team did not know who was receiving active drug or placebo (a pretend drug) and aimed to determine whether Tominersen actually does slow down the progression of HD in a clinically meaningful way.

In March 2021, Roche announced that dosing would be permanently halted in the Generation HD1 trial and paused on the Gen Extend trial. This decision was not based on any new emergent safety concern, but on a broad risk/benefit assessment of treatment arms compared to the placebo arm over time in the Generation HD1 data.

In January 2022 it was announced that the Gen Extend trial would complete in March 2022. This decision came after a post-hoc analysis of the Generation HD1 trial suggested that Tominersen *may* have a potential benefit in a subgroup of patients. We therefore completed the Gen Extend trial in March 2022.

Since then, Roche have been designing a new double blind, placebo controlled trial which is going to look at a younger adult population with prodromal and early manifest Huntington's disease, which is basically those with Huntington's disease right around the time abnormal movements begin to appear. This trial is aiming to recruit 360 participants across 4 continents who will receive either 60mg or 100mg of Tominersen or a placebo every 4 months for a total of 16 months of treatment and monitoring.

We are a site recruiting to this new trial and about to start this. If you want to hear more or are interested in participating, please contact Katie on kera2@cam.ac.uk or 01223 331141

SOMCT03 – a drug trial looking to treat chorea symptoms in HD

Funded by SOM Biotech

Katie and Dimitrios started recruiting in February this year to a new pharmaceutical drug trial at our site in Cambridge. SOM Innovation Biotech, a biopharmaceutical company developing treatments for rare neurological diseases, have designed a trial to look at a potential treatment for chorea, which are the involuntary movements in Huntington's disease, with a drug named SOM3355.

This trial is being conducted in 7 countries across Europe, including the UK and aims to recruit 130 participants in total. This is a double blind randomised trial meaning participants do not know whether they are receiving active drug or placebo (a pretend drug) and nor do the trial team.

This trial involves taking the medication or placebo for 12 weeks and coming in for different assessments, some that may be familiar to those who attend clinic as well as a few clinical measures like vital signs, blood samples and assessments of the heart on an ECG machine.

The trial closed to recruitment at the end of 2023 so we hope to provide an update on the results of the trial in the near future.

SOM BIOTECH

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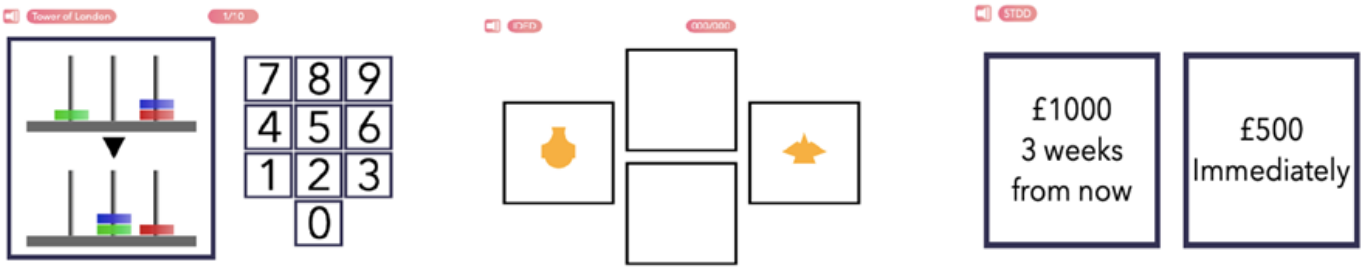
DOPA-HD

Funded by NIHR Biomedical Research Centre – Dementia theme

This study initially started in 2018 and stopped in 2020 due to COVID-19, however, since spring 2022 we have restarted DOPA-HD. DOPA-HD focuses on the role of the brain chemical dopamine, which is known to play an important role in coordinating movements as well as helping with certain aspects of thinking such as memory, attention, and planning. We know that dopamine contributes to some of the motor features of HD, therefore HD is often treated with drugs which reduce dopamine transmission in the brain. However, we do not know how these drugs affect the way people with HD think.

DOPA-HD, investigates the immediate effects of increasing and decreasing levels of the brain chemical dopamine on cognition in HD. During DOPA-HD, participants visit our centre on four separate occasions, during which they take one of the following: a drug which activates the dopamine receptor (effectively increasing dopamine levels), a drug that blocks the effects of dopamine (effectively decreasing dopamine levels), both drugs at the same time (so no change in dopamine levels), or a placebo. After a break of 90 minutes, participants undergo some computer based cognitive tasks.

If you are interested to hear more about this study, please contact Amy on ahe28@cam.ac.uk or 01223 727489



A screenshot of some of the assessments participants are asked to complete on the DOPA HD study

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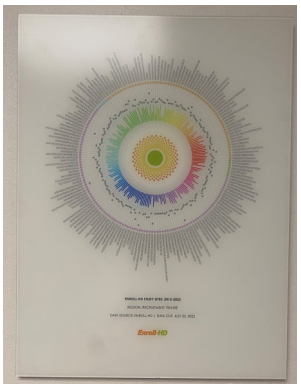
ENROLL-HD

Funded by Cure Huntington's Disease Initiative

The Enroll-HD study is the world's largest observational study and celebrated it's 10th anniversary in 2022. The study involves around 21,000 participants from over 179 hospitals and 23 countries. In Cambridge, we have around 113 participants who take part. During 2023 we completed 76 follow up visits and we recruited 17 new participants.

Study visits involve completing questionnaires, thinking and memory tests and giving a blood sample along with the normal assessments that are completed in clinic. An anonymised version of the data from Enroll-HD is available to all researchers from any of the sites involved in this work. This means that we have access to information about a very large number of people with HD, from all around the world, that can help us to answer questions about HD in a fast and efficient way that was not possible before.

We have started a new sub-study, **the plasma collection study**, which is an annual blood test across 5 years. We currently have 22 participants in this study. We are hoping to start another sub-study called the **Later Stage Assessments study**, this seeks to develop a series of assessments that are more appropriate for patients with advanced HD. This will hopefully start later this year. If you are eligible, you may be asked to participate in either or both sub-studies when you next come to clinic.



If you are already enrolled and would like to contact us about your follow up appointment, or would like to participate, please contact Amy on ahe28@cam.ac.uk or 01223 747489

HD Clarity

We are involved in the HD Clarity study, which is a multi-site cerebrospinal fluid (CSF) collection study in HD patients. CSF is an ideal fluid compartment for assessing HD biomarkers due to its proximity to the brain. It is collected via a lumbar puncture and can facilitate the identification and development of new biomarkers, as well as exploration for potential targets for intervention. This study also works in collaboration with Enroll HD and we are actively recruiting to HD Clarity.

If you would like to hear more about this project or would like to participate, please contact Katie on kera2@cam.ac.uk or 01223 331141

HUNTINGTON'S DISEASE NEWSLETTER

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Sleep in HD

Funded by Association of British Neurologists

ASSOCIATION OF BRITISH NEUROLOGISTS

Zanna is continuing her work in sleep in Huntington's, looking at whether improving associated sleep problems might help mitigate symptoms, such as problems with attention, memory and mood, or even slow disease progression.

This has centered around completing a longitudinal study that has been running in the group since 2009, where we have been studying sleep in HD gene carriers using motion-sensitive wrist devices, blood tests for the sleep hormone melatonin, and hospital sleep studies where we measure EEG (brainwaves) overnight.

This work is at an exciting stage, as we have now completed the study and are aiming to publish some important findings imminently. Zanna is now wearing glasses having finished analysing 23,000 pages of sleep brainwaves! A huge thank you to everyone who came in for their follow up overnight sleep study last year, and thanks also to those who are now undertaking comparative home sleep recordings using specialist headset devices (pictured below). It is hoped that these devices will make our sleep research faster and more convenient for participants going forward.

Last year we made a short YouTube video about the study if you'd like to know more (snapshots below):

https://www.youtube.com/watch?v=7w3ywQ4c-WY

We are hoping to take this work forward into studies of new sleep therapies in the near future. If you think you may be interested in this phase of our research, please contact Zanna on zv214@cam.ac.uk

Snapshots from our recent NIHR video showing electrodes used to record sleep brainwaves and blood samples to measure the sleep hormone melatonin

The Dreem3 headsets and app we are currently using to record sleep at home

HUNTINGTON'S DISEASE NEWSLETTER

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Social Decision-making in Huntington's Disease

Social interactions are at the core of most people's everyday life. Processing those interactions happens very quickly and seemingly automatically, however when broken down they require a large variety of complex skills such as understanding social cues and nonverbal communication of thoughts and feelings. Research suggests that some individuals with HD struggle with those skills leading to difficulties when navigating social situations.

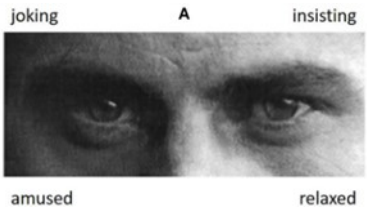
The aim of this project is to understand what this problem of social functioning looks like and any underlying changes in specific thought processes driving this problem.

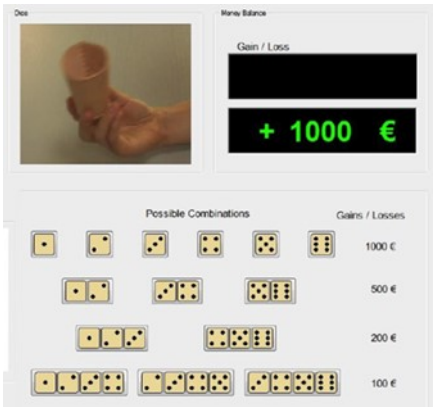
We are also trying to better understand the effect poor social functioning can have on everyday life. For example, we are interested to see how social functioning relates to the feeling of loneliness and social isolation.

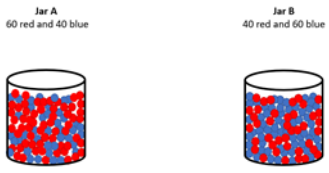
Participation involves two visits to our centre, each lasting approximately 1.5 hours. On both visits participants are asked to complete a number of computer tasks on social functioning and different cognitive tests as well as an array of questions about the individuals' everyday experiences.

As of now we have 28 participants of which 15 are HD gene carriers with disease symptoms, 13 are HD gene carriers without symptoms and 7 controls without the HD gene.

If you would like to participate in this study, please contact Miriam on ms2709@cam.ac.uk or 01223 767379







A screenshot of some of the assessments participants are asked to complete on the Social Decision making study

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Loneliness in neurodegenerative disease affecting social cognition

Loneliness and social isolation have been a topic of interest for research during the last decade, which has led to a better understanding of the relationship between loneliness/social isolation and poor mental/ physical health. This in turn gave rise to many different interventions and organisations trying to reduce loneliness in the general public. It has also been established that individuals with a disability are disproportionally affected by loneliness. However, very little research has been done on loneliness in rare neurodegenerative diseases.

Understanding loneliness and social isolation among those diseases might be of particular importance as affected individuals are especially reliant on a good social network for support. Further, many of those rare neurodegenerative diseases are associated with problems of social functioning which could worsen the problem of loneliness and social isolation.

This project aims to explore loneliness and social isolation in Huntington's Disease, as well as in some other similar disorders. It aims to better understand how loneliness and social isolation presents in individuals with these diseases and how these problems relate to social functioning and areas of everyday life.

The study involves a number of questionnaires which are completed online. Participation takes approximately 20 minutes and can be done from any electronic devices (E.g. phone, tablet, computer). Anyone who is HD gene positive is welcome to participate regardless of whether disease symptoms are present or not. Furthermore, participants do not need to experience loneliness to participate in this study, as we would like to get as many different perspectives on this topic as possible.

As of now 101 participants have completed the study of which 12 are HD gene carriers without symptoms and 17 are HD gene carriers with symptoms.

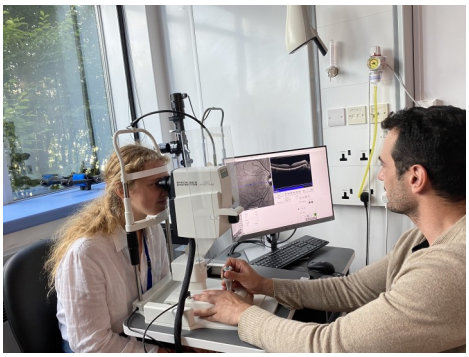
If you would like to participate, please scan the QR code or follow this link https://redcap.link/20bzhw5r , both will direct you to the questionnaires. If you have any questions or would like to receive an e-mail with the study link, please contact Miriam on ms2709@cam.ac.uk or 01223 767379

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

The EYE-HD study: Can we study the back of the eye to track disease progression in HD?

We want to explore whether there is a subtle but measurable abnormality in the eyes in HD. We understand that Huntington's disease is a condition where the abnormal protein is found in every cell of the body. This study will assess eye functions but especially the anatomy of the retina and how this might get affected over time in patients with Huntington's disease. We know that patients with HD do not have poor vision so what we are looking for is a very subtle abnormality. To achieve this Dimitri will be using a non invasive technology called Optical Coherence Tomography (OCT) that uses light to capture micrometer pictures of the retina. Participating in the study involves attending the hospital campus for the clinical and eye assessments at a special facility (not the clinic itself but nearby). The eye assessments are not too dissimilar to the ones usually done at an optician's annual eye check. You may be asked if you would like to participate at your clinic appointment, however if you are interested please feel free to contact Dimitrios on da539@cam.ac.uk or 01223 767761



In addition, we have another eye related project which looks at a thing called fixation loss. Fixation loss describes the impaired ability to look at a non-moving target such as the tip of a pen for a prolonged period of time. While healthy people would be able to stare at a target for a long duration without moving the eyes, HD patients we think may have irrepressible minor eye movements taking their eyes away from the fixation target. The aim of the project is therefore to see if this is true, as such subtle changes may help us diagnose the condition sooner.

A high-tech eye tracker will be used in order to precisely assess fixation loss with the hope to bring this to the clinic and further aid the diagnostic process.

It should also be stressed that these subtle changes in eye fixation cause no symptoms in the HD individual.

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

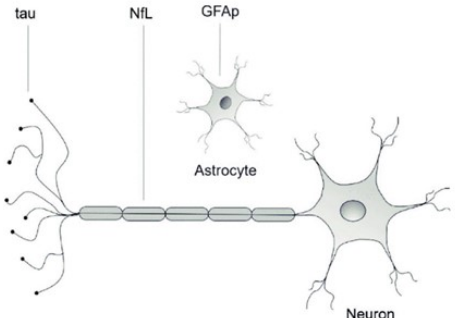
Fluid Biomarkers in HD

This work has been made possible from a donation from a HD family—thank you!

Huntington's disease leads to the progressive loss of nerve cells. Due to the genetic pathology of HD, we have a unique opportunity to investigate potential early signs of neurodegeneration in individuals who carry the HD-related gene but have not yet shown symptoms of manifest disease. One way to quantify neurodegeneration is by measuring the levels of certain proteins in an individual's blood that are known to increase as a result of neuronal injury or death. Examples of such fluid biomarkers include neuro-filament light (NfL), glial fibrillary acidic protein (GFAP), and tau, all of which Natalia has been working on in our group.

Specifically, we are interested in the potential use of these biomarkers as prognostic tools in the diagnosis of disease onset and progression. By looking at the behavior of these proteins in gene carriers who exhibit an earlier disease onset compared to those who remain premanifest for longer, we can learn more about how neurodegeneration progresses in HD. We can then compare the levels of fluid biomarkers with cognitive and motor assessments. Any correlations we find can help us further understand how these biomarkers behave in the years leading up to conversion from a premanifest to manifest disease state.

Thus, this project holds both clinical and research utility. HD gene carriers are diagnosed as manifest primarily based on evidence of motor features. Identifying fluid biomarkers can offer clinicians a more reliable and accurate way to predict when gene carriers may expect disease onset. From a research perspective, fluid biomarkers can be used as a measure of treatment response in disease-modifying drug trials, in that if an agent slows down the disease process then the level of these proteins should go down (e.g. see the FELL HD trial on p5). Linked to this is the fact that fluid biomarkers have the potential to facilitate earlier treatment intervention for gene carriers with the aim of slowing disease progression.



Types of fluid biomarkers from neurons and astrocytes (type of glial cell)

HUNTINGTON'S DISEASE NEWSLETTER

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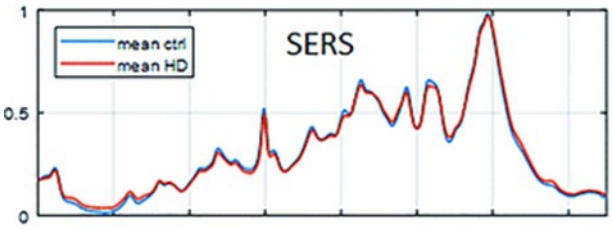
Surface-Enhanced Raman Spectroscopy (SERS) in HD

In this study we have already collected blood samples and clinical data from over 100 patients and healthy controls, and are currently scheduling time with our collaborators in the Chemistry Department at Southampton to analyse our samples. We hope to be able to show that there are subtle changes in the blood that are linked to Huntington's Disease, and that using this, we can track disease progression. If this technique is shown to work, it would help us with the development of treatments for Huntington's Disease by being able to measure how much of an impact they are having on the disease.

We are using a chemical spectroscopy technique called Raman Spectroscopy. This involves shining a laser into the blood. As different substances absorb different amounts of different light wavelengths, spectroscopy can be used to tease apart differences in the composition of your blood. This outputs a spectra. We will compare these spectra to clinical outcome measures. This builds on previous work done in our lab that has already been published.

A Raman microscope that is used for the analysis of our samples



Average surface-enhanced Raman Spectra for healthy controls vs HD participants

The Cambridge Brain Bank

You are probably familiar with organ donations of the heart, kidneys or liver to sustain the health or even the life of people in need. Brain donation for research is a precious and unique gift. Scientists can learn and understand more about disease processes when they are able to work on donated tissue. The donation of a brain and other parts of the nervous system is a big decision and needs much discussion. Advice is available from the Cambridge Brain Bank team who would be very happy to talk through any concerns you or your family may have.

You can contact the team on telephone number 01223 217336 or email addtr.cambridgebrainbank@nhs.net for further information as well as visiting the website: https://www.cuh.nhs.uk/our-research/get-involved/donate-body-to-medical-science/

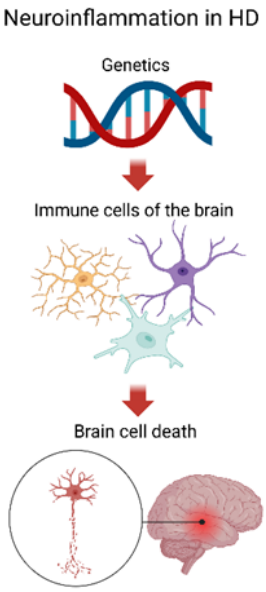
Over the last 8 years we have had 13 donations from HD patients. We would like to thank the patients and their families for this.

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Neuroinflammation in Huntington's disease

Our brain's immune system is designed to protect us from harm and is essential for normal brain function. In Huntington's disease (HD) this immune system may be slightly abnormal and may be causing more harm than good. Reducing inflammation in HD may therefore help delay the progression of the disease. In this study we have sought to investigate the cause of this inflammation as well as novel ways to visualise inflammation in the brain.



The first part of this project will involve looking at the levels of inflammation in different parts of the brain using a variety of techniques. The second part of this project will utilise state-of-the-art positron emission tomography (PET) imaging as a way to observe immune cells in the brain in real time. Recent advances in PET technology allows for more sensitive and accurate imaging, which will be applied for the first time in HD research. This will be valuable in expanding our knowledge around the disease and could assist future clinical trials in

Measuring mutant huntingtin in Huntington's disease

As we know, HD is caused by a mutation in the *huntingtin* gene. Normally this *huntingtin* gene tells a person's cells to produce the normal Huntingtin protein (HTT). In patients with HD however, this gene is faulty and produces a toxic form of the protein, called mutant huntingtin (mHTT). Currently there is no cure for Huntington's disease. Promisingly, there are new drugs on the horizon. These drugs work by lowering the amount of the toxic mHTT protein that a patient produces in their cells (see p6). Unfortunately, scientists do not yet have a very accurate way of measuring how much these drugs lower the amount of toxic mHTT protein in the brain.

Therefore, HD scientists need a better way of measuring the amount of the toxic mHTT protein present in HD patients.

We are aiming to develop a new way of tracking the amount of mHTT protein in the brains of patients with HD. To achieve this goal we will use a medical imaging technique called **positron emission tomography (PET)**. This technique attaches a radioactive tag to the toxic mHTT protein. This radioactive tag allows us to see inside the brain of patients with HD and measure how much of the toxic protein is present. We hope PET imaging techniques will give HD scientists an accurate way of telling how much mHTT protein is present in the brains of HD patients, thus creating a better way to test new HD drugs.

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Publications in 2022

Stoker TB, Mason SL, Greenland JC, Holden ST, Santini H, Barker RA. Huntington's disease: diagnosis and management. Pract Neurol. 2022 Feb;22(1):32-41. doi: 10.1136/practneurol-2021-003074. Epub 2021 Aug 19. PMID: 34413240.

This paper looks at how we diagnose HD. Although the diagnosis of HD is usually straightforward, unusual presentations can occur, and it can be difficult to know when someone has transitioned from being an asymptomatic carrier into having the disease. A growing number of conditions can mimic HD, including rare genetic causes, which must be considered in the event of a negative HD genetic test. Patients are best managed in specialist multidisciplinary clinics, including when considering genetic testing.

Pircs K, Drouin-Ouellet J, Horváth V, Gil J, Rezeli M, Garza R, Grassi DA, Sharma Y, St-Amour I, Harris K, Jönsson ME, Johansson PA, Vuono R, Fazal SV, Stoker T, Hersbach BA, Sharma K, Lagerwall J, Lagerström S, Storm P, Hébert SS, Marko-Varga G, Parmar M, Barker RA, Jakobsson J. Distinct subcellular autophagy impairments in induced neurons from patients with Huntington's disease. Brain. 2022 Sep 14;145(9):3035-3057. doi: 10.1093/brain/awab473. PMID: 34936701; PMCID: PMC9473361.

In this paper we worked with a group in Sweden to make nerve cells (so cells induced neurons) from the skin cells of people with Huntington's using a special technology and by so doing we can (to some extent) model looking at the patients brain cells in the dish. We then studied these induced neurons and found they had very specific defects in certain parts of these nerve cells in autophagy- which is a process involved in getting rid of huntingtin from the cells and which we are targeting in the FELL-HD trial

Harris KL, Mason SL, Barker RA. Exploring the predictors of financial impairment in Huntington's disease using the Enroll-HD dataset. J Neurol. 2022 Jul;269(7):3501-3510. doi: 10.1007/s00415-021-10929-4. Epub 2022 Feb 14. PMID: 35165768; PMCID: PMC9217841.

This paper looks at a longitudinal data set to determine the prevalence of financial dysfunction in HD, and the demographic and clinical predictors of such impairments. Financial impairment was found to be common in HD gene carriers and some predictors of this were identified.

Denis HL, Alpaugh M, Alvarez CP, Fenyi A, Barker RA, Chouinard S, Arrowsmith CH, Melki R, Labib R, Harding RJ, Cicchetti F. Detection of antibodies against the huntingtin protein in human plasma. Cell Mol Life Sci. 2023 Jan 18;80(2):45. doi: 10.1007/s00018-023-04687-x. PMID: 36651994; PMCID: PMC9849309.

This study was led from the lab of Francesca Cicchetti in Quebec and sought to see whether we could measure antibodies against the protein seen in HD, namely huntingtin. We found that they could be found in the blood and that the levels of them varied depending on the disease stage.

Owen NE, Barker RA, Voysey ZJ. Sleep Dysfunction in Huntington's Disease: Impacts of Current Medications and Prospects for Treatment. J Huntingtons Dis. 2023;12(2):149-161. doi: 10.3233/JHD-230567. PMID: 37248911.

This paper looks at sleep dysfunction in HD. Increasing evidence suggests that such dysfunction not only impairs quality of life and exacerbates symptoms but may even accelerate the underlying disease process. Despite this, current HD treatment approaches neither consider the impact of commonly used medications on sleep, nor directly tackle sleep dysfunction. This review discusses approaches to these two areas.

HUNTINGTON'S DISEASE NEWSLETTER

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Websites of interest

Barker Williams-Gray Lab

UNIVERSITY OF CAMBRIDGE

www.thebarkerwilliamsgraylab.co.uk/

Twitter: @PDandHDLab

HD BUZZ

https://en.hdbuzz.net/

HUNTINGTON'S DISEASE ASSOCIATION

https://www.hda.org.uk/

HDYO

Huntington's disease youth organisation

https://en.hdyo.org/

Donations

If you would like to donate to any of our research projects, please do contact Shaline Fazal on sf618@cam.ac.uk or 01223 331141

You can write to us at the below address: John Van Geest Centre for Brain Repair, E.D. Adrian Building, Forvie Site, Robinson Way, Cambridge, CB2 0PY