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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Anne Rosser, Cardiff University

EHDN research highlights

Laura Spinney

For this edition of the newsletter we've been flicking through the rollerdeck of EHDN-funded research projects to bring a selection of them to your attention. Most of these projects are listed on the EHDN website but are so well-hidden that you would be forgiven for not realising they exist (the website will soon get a facelift).

You might not be aware, for example, that Anne Rosser of Cardiff University and her team are setting up a network of six British university hospital sites whose goal is to collect fetal tissue carrying the HD mutation. They want to know if the HD mutation affects the development of the striatum—a part of the brain that is affected in the early stages of HD. This means studying the anatomy, gene expression profile and cellular characteristics of fetal brain tissue. Collecting such tissue requires that the appropriate procedures are followed—not least the obtaining of consent by a specially trained research nurse. It's those procedures, across the six sites, that this project aims to put in place.

Ed Wild, University College London

Meanwhile, at University College London, Ed Wild and colleagues have embarked on a pilot study using MRI to look at what happens to the flow of cerebrospinal fluid (CSF)—the fluid that bathes the brain and spinal cord—in HD. Animal studies have shown that this flow may be altered in HD, a finding that needs to be investigated further because altered CSF flow could affect the action of any therapeutic drugs that are designed to be injected into the CSF.

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CSF flow can, in theory, be studied non-invasively using an imaging technique called phase contrast MRI, that was originally developed to measure blood flow in the brain. In PHASE1-HD, as the project is called, Wild's group will adapt the technique to measuring CSF flow and then test it in 10 HD patients and 10 healthy controls, with a view to testing it in larger groups in the future.

One key goal of HD research at present is to find reliable markers of disease progression. At the Institute for Psychiatry and Neurology in Warsaw, Poland, Katarzyna Jachińska and her team are investigating whether transcranial sonography (TCS) could provide such a marker. TCS is a relatively new form of imaging that uses sound waves to noninvasively probe structures within the brain, and that has proved sensitive enough to detect subtle changes in those structures over time.

Katarzyna Jachińska, Institute for Psychiatry and Neurology, Warsaw

In their project, Jachińska and colleagues will prospectively study a group of HD patients in an attempt to correlate structural brain changes, as measured by TCS, with evolving clinical symptoms such as depression and apathy. There is evidence from Parkinson's disease patients, for example, that changes in the TCS response of a brainstem structure called the Raphe nuclei correlate with the onset of depression. If the Polish researchers find a similar correlation in HD, then in theory TCS could be used to predict the onset of such symptoms, which in turn would mean they could be treated earlier. This could be important because depression is a common psychiatric symptom of HD, as well as a possible side effect of dopamine-depleting drugs that are prescribed to treat the involuntary movements associated with the disease. Pending the outcome of the trial, TCS could also prove useful in clinical trials evaluating experimental therapies for psychiatric symptoms.

Another potential biomarker of HD is, surprisingly, brown fat. Weight loss is a big problem for HD patients, and research in animal models has suggested that brown fat, a highly metabolically active form of adipose tissue, could be dysfunctional in the disease. Katrin Lindenberg at Ulm University in Germany is leading a team of clinicians and imaging experts who have developed a way of tracking the degeneration of brown fat *in vivo*, in mouse models of HD, using MRI. The next step for Lindenberg's team will be to test the technique in HD patients. If they can show a clear correlation between brown fat degeneration and other markers of HD progression, then brown fat imaging could provide another useful biomarker of the disease.

Katrin Lindenberg and Patrick Weydt, Ulm University

When doctors assess motor impairment in HD patients, they do so using standardised clinical scoring systems such as the Unified Huntington's Disease Rating Scale. However experienced they are, though, there is always some variability between the assessments of different clinicians, and even within the assessments of the same clinician, when applying the scale to a given patient. What if technology could be harnessed to reduce that variability? That is the goal that Patrick Weydt of Ulm University and colleagues—both clinicians and engineers—have set themselves, in an EHDN-funded pilot study.

Partially automated systems for assessing motor performance are already available, but they are expensive and sometimes complicated to use. Weydt's group is testing commercially available optical and gravitational motion sensors—the kind that are already built into video game consoles—as a cheaper, more use-friendly alternative. They've also devised a prototype app that uses the information acquired by motion sensors in standard smart phones to detect and quantify hand and limb movements, and they are currently testing these in a group of HD patients and healthy controls. If the app proves reliable and effective, it will be useful in clinical trials for measuring drug effects on motor symptoms more reliably than is currently possible.

Information about other EHDN-funded research projects can be found here: https://www.euro-hd.net/html/projects/proposals/announcements
Summaries of a selection of scientific articles generated by EHDN-funded research can be found here: https://www.euro-hd.net/html/disease/summary

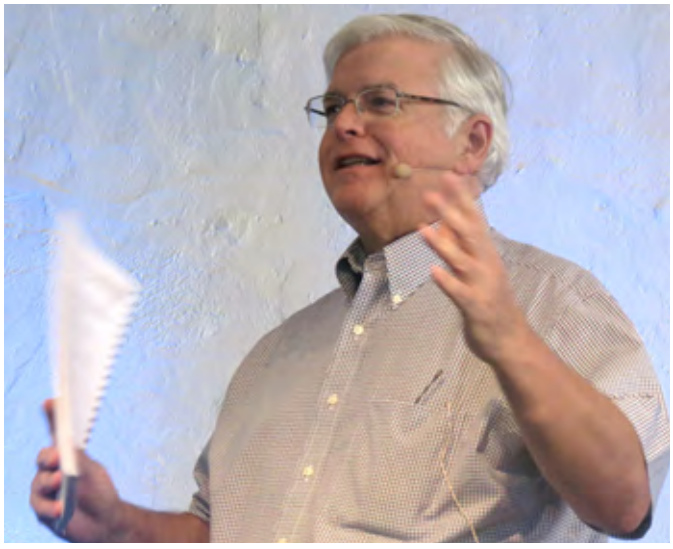
HD Therapeutics 2014: a progress report

Michael Orth,
Central Coordination

Among many interesting presentations at the HD Therapeutics conference in Palm Springs in February, two stood out: the first results of a genome-wide association study into genetic factors affecting age of onset in HD, and a new method for evaluating experimental treatments in humans.

About half of the variability in the age of onset of HD is determined by the HD mutation itself, but most of the remaining variability is the result of "natural" variation in the DNA sequence—variation in the physiological range, that is, that affects such traits as eye colour and height. When the HD mutation is present, that natural variation may modulate its effects—either enhancing or reducing them—and in so doing influence the age at which the disease manifests itself.

So far, candidate gene studies have failed to produce strong, reproducible evidence for such genetic modifiers, but some of these studies have been statistically underpowered, or did not stratify the populations studied sufficiently. The Genetic Modifiers of HD consortium, whose work was presented by James Gusella of Harvard Medical School, took data made available by large databases such as Registry, COHORT and PREDICT-HD, and used them to map one million letters of the genetic code where differences between healthy individuals are known to occur.



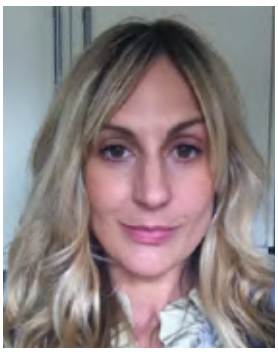
James Gusella

The consortium looked for any correlation between these differences and the age at which the first motor signs of HD were noticed in HD patients. Based on data from more than 4,000 patients, they were able to identify associations between age of onset and variability on chromosome 15 that were stronger than might have occurred by chance. Further work is needed to identify which loci on chromosome 15 are responsible for these effects, but the finding is the first convincing demonstration that natural genetic variation can indeed affect the course of HD.

Andreas Weiss

The second presentation of note was given by Andreas Weiss of Rome-based biotech company IRBM Promidis. Among the most promising hopes for better treatment of HD are gene silencing therapies that work by selectively suppressing the mutant allele of the huntingtin (*HTT*) gene while leaving the healthy *HTT* allele alone. In animals, the effects of such experimental treatments can be measured directly in brain tissue, but this is not possible in humans. Alternative, indirect methods of evaluating them are needed for when those treatments move into clinical trials.

Weiss presented his group's research on just such a method, which measures the huntingtin protein in human cerebrospinal fluid (CSF). They have fine-tuned this method so that they can now detect huntingtin in very low concentrations in the CSF of HD patients. More work is needed to test how robust the method is, and how levels of huntingtin in the CSF relate to its levels in the brain, nevertheless the finding represents an important advance in the development of measurement tools for use in future clinical trials.



EHDN is collaborating on Pride-HD, a pridopidine trial

Jenny Townhill,
Central Coordination

The EHDN is collaborating with Teva Branded Pharmaceutical Products on Pride-HD, a phase 2, global trial of the investigational drug pridopidine, and has approved the trial protocol. Pride-HD is sponsored by Teva and supported in its operational aspects by the EHDN and the Huntington Study Group.

The main aim of the Pride-HD study is to assess the effects of pridopidine on the motor symptoms of HD after six months of dosing, using the Unified Huntington's Disease Rating Scale–total motor score (UHDRS-TMS). The study will explore a range of doses. It will also examine the effects of pridopidine on the Physical Performance Test, and the drug's safety and tolerability across a range of doses for the duration of the trial, in HD patients. The effects of pridopidine on several additional endpoints, such as Q-motor, Problem Behaviours Assessment, Clinician's Interview-Based Impression of Severity and the Cognitive Assessment Battery, will also be studied, along with the drug's pharmacokinetic properties.

The EHDN's Clinical Trials Task Force and Scientific and Bioethics Advisory Committee has reviewed the scientific and ethical content of the Pride-HD protocol. The study aims to recruit 400 participants at around 50 study sites in the US, Canada, Russia, Australia and eight countries in Europe. Recruitment has started in several countries and is expected to be completed in 2015.

Patients who might be eligible to participate in the trial must be over 21 years of age and have a clinical diagnosis of HD. They will be assessed for a number of additional inclusion criteria before they can enroll. A companion or caregiver must also be available and willing to report on how pridopidine is affecting the patient for the duration of the trial.

Ralf Reilmann, Pride-HD study investigator

More information on Pride-HD can be found at:
http://clinicaltrials.gov/ct2/show/NCT02006472
and on the EHDN website:
https://www.euro-hd.net/html/projects/pride

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EHDN elections

Voting opens on 28 July for new members of the EHDN's Executive Committee (EC) and Scientific and Bioethics Advisory Committee (SBAC). There are currently four vacant seats on the EC and six vacant seats on the SBAC. Those elected will serve on their respective committees for a four-year term, at which point they will rotate off (unless they stand for re-election and their mandate is extended) and new elections will be held. All regular members of the network are encouraged to vote, and voting, once it opens, will take place here. It will remain open until 31 August and the results of the elections will be announced at the EHDN plenary meeting in Barcelona (19-21 September).

Update: Enroll-HD

Ruth Fullam, European Manager, Enroll-HD

Six months into the European start-up of Enroll-HD, 20% of all Registry sites have now transitioned or are in the process of transitioning to the new study.

The pace of transition is accelerating after an initial period during which it was deliberately kept slow in order to test novel procedures. Around eight sites are now seeing their data closed out each month, prior to moving across to the new system. In the months ahead, we expect the pace to pick up still further.

To date, 18 European sites have been closed out in Registry and activated in Enroll-HD, while recruitment in Europe already represents 10% of the global total (more than 2,300) and is growing rapidly. Germany has seven activated Enroll-HD sites, the UK has eight and the first Polish and Italian sites have begun recruiting. In the next three months, more British, German and Italian sites are expected to launch in Enroll-HD, while Poland will become the first country to fully complete the transition. The first Dutch, Belgian, Swiss, Austrian, Spanish and Danish sites will enter the transition process in the same period. France will enter the process around October; its application is currently with the regulatory authorities.

Sweden, Norway, Russia and Portugal will follow in the fourth quarter of 2014, though some sites in those countries may enter the process earlier, and the ultimate goal is to have all countries in Europe engaged with the process before 2014 is out. The more countries that are "transition-ready" the better, because it means the transition team has maximum flexibility to fill transition slots as and when they become available. Realistically, the scale of the task means that some sites will not enter the process until 2015, however investigators who are keen to start earlier should review the status of their contract. Once a contract is executed, and ethical review board permission has been obtained, a transition slot can be scheduled for a site.

Of the more than 130 contracts that sites must sign with Enroll-HD, most have now been sent out and almost half have been or will soon be executed. Site investigators are reminded that they can check the status of their contracts by contacting Enroll-HD's contract manager, Jonathan Miles (jonathan.miles@quintiles.com), who would also be happy to answer any contract-related questions. Any such communications should be copied to the relevant language area coordinator (LanCo). The LanCos keep track of activity in their regions and know the timeframe of transition for each site in their remit.

Further updates and training will be provided at regional site investigator meetings and at the EHDN plenary meeting in Barcelona in September. We look forward to seeing you at these events and to welcoming you into Enroll-HD.

For further information, please contact EnrollHD@quintiles.com or visit www.enroll-hd.org

Roundup: funding news

Fionnuala Margreiter, Grant Manager

ECRD 2014

In May the EHDN was present at the 7th European Conference on Rare Diseases & Orphan Products (ECRD) in Berlin, which was attended by more than 750 people from 40 countries. The rare diseases community represents opportunities for collaborative research projects, and the EHDN would like to encourage its members to increase their participation and visibility in that larger community in order to be able to take advantage of those opportunities. The next ECRD meeting will be held in Edinburgh in mid-2016. Details will be published in the newsletter.

Horizon 2020: call for rare diseases funding

The European Union's research and innovation funding programme, Horizon 2020 (H2020), has launched a two-stage call for research proposals on rare diseases.

Most of the 6,000-8,000 rare diseases lack therapies, though many are life-threatening or chronically debilitating. This call welcomes proposals that address one or more of the following: development of new or improved therapeutic approaches, repurposing of existing therapies, preclinical research, animal model development and good manufacturing practice production. The treatments to be developed may range from small molecule to gene or cell therapy.

Proposals requesting a contribution from the EU of between four and six million euros will be considered. Successful proposals will contribute to the objectives of, and follow the guidelines and policies of, the International Rare Diseases Research Consortium.

The deadline for the first stage of the call is 14 October 2014 and more information is available here or via your National Contact Person for H2020.

COST Actions

COST (European Cooperation in Science and Technology) is an intergovernmental framework designed to help coordinate research across Europe. It does so in part via Actions, networks centred around nationally-funded research projects in fields that are of interest to at least five COST countries.

Though COST does not fund research itself, it provides support for networking activities carried out within Actions. These include meetings, workshops and training schools. COST accepts applications for Actions from researchers, NGOs, industry and SMEs. It offers financial support averaging €130,000 per year for four years, and the next deadline for applications is expected to be in March 2015.

For further information or advice on how to make the most of funding opportunities, please contact Fionnuala: fionnuala.margreiter@euro-hd.net

Searching for therapies, one step at a time

Bernhard Landwehrmeyer, Chair, Executive Committee

At the EHDN plenary meeting in Barcelona in September, Bernhard Landwehrmeyer will stand down as chair of the Executive Committee. Though he will remain on the EC and very active in the network, we asked him to look back on a productive career and 10 years at the helm of a unique organisation.

My first real exposure to Huntington's disease as it is lived by patients was in 1994, when I had the opportunity to accompany Nancy Wexler and Anne Young to Lake Maracaibo in Venezuela. I was struck by the tremendous impact the disease had on these people who had hard lives anyway. They were fishermen, simple people. Many of them lived in shacks, and this deadly disease imposed a terrible additional burden on them that they carried with great bravery.

There was one incident I will never forget. We visited an old lady whom we found starving and emaciated. She hadn't eaten for two days. Her 16-year-old granddaughter was supposed to be looking after her, but this young girl also had to look after her younger siblings since one of her parents had HD, and the only way she could support them all was by prostituting herself. She appeared while we were with her grandmother, and apologised for not having come earlier, but as she explained, she simply wasn't able to be everywhere she had to be, while also earning the money she needed to feed her family.

That visit left a powerful impression on me, and I found it extremely motivating. The previous year, 1993, I had gone to work as a postdoc in Anne Young's lab at Massachusetts General Hospital in Boston. By then, in my career as a neurologist, I had reached the point where I wanted to study the pathological mechanism from first principles, so to speak, and so I had become interested in monogenic diseases. Anne's interest was in HD, which is why I applied to work in her lab. Serendipitiously, in March of that year, Jim Gusella, Marcy MacDonald and others identified the huntingtin gene and mutation, and I became involved in efforts to visualise the distribution of huntingtin mRNA in brain tissue, using a technique called *in situ* hybridisation histochemistry. Those were exciting times!

Bernhard Landwehrmeyer and Nancy Wexler at the 2008 EHDN plenary meeting in Lisbon, Portugal

After three years in the US I returned to Germany, to Freiburg where I set up an HD clinic, and in 1999 I was recruited by Ulm University where I still work today. My first task in Ulm was to set up a trial of a drug called riluzole that, it was felt, could potentially modify the disease process in HD. It had to be a long trial, lasting three years, and it had to recruit a large number of patients, over 500, which meant that we required the participation of a number of sites in different European countries.

This posed something of a logistical challenge, but we pulled it off. The trial was called the European Huntington's Disease Initiative, and while it was still underway I and others began to think that it would be a waste to let the infrastructure we had created wither away after the trial had ended. How could we maintain that infrastructure to support future clinical trials? we asked ourselves. In 2003, I happened to meet Robi Blumenstein of CHDI at a Gordon Research Conference in Tuscany. We talked, the talks carried on after the conference had ended, and the result was the CHDI-funded European Huntington's Disease Network.

> *"If I had to name one achievement of the EHDN that I'm most proud of, it would have to be our realisation that we weren't going to stumble on a miracle cure."*

Rather, we took the view that it was necessary to approach the disease rationally, advancing step-by-step along a path of learning that would involve many people

from many different disciplines working in parallel and collaboratively. Patients understandably feel frustrated sometimes, when they see our approach, because for them time is running out, but I believe that this is the best way we can help them in the long run.

We've come a long way. We can already suppress mutant huntingtin in the brains of transgenic mice very effectively. A mouse brain is much smaller than a human brain, however, and delivering these therapies will be our next big challenge. Our goal for the next 10 years, with that of our colleagues beyond Europe, should be to translate our successes to date into effective therapies for patients. That, in my view, will mean combining some of the approaches that are currently working so well in mice. It's a big ask, but with the help of the network we have put in place, I think we can do it.

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Twitch: a postscript

In 2010, when she was 16, Kristen Powers thought it would be cool to make a documentary (we reported on it in our issue number 20, November 2013). She wanted to show people what it was like to live in an HD family, under the threat of developing the disease herself. Within four years, she had raised $40,000 and made a film about her personal experience of getting tested for the HD mutation. The result, Twitch, will be shown at the EHDN plenary meeting in Barcelona in September (please see programme for more details). Kristen wants it to be distributed as widely as possible, so that it can help reduce the stigma surrounding HD. To organise a screening, contact her at: kristen_powers@ymail.com

Dates for your diary

Save the dates for

- HD2014: "The Milton Wexler Celebration of Life" symposium, Cambridge, Massachusetts, USA, 6-9 August 2014
- EHDN2014 in Barcelona, Spain, 19-21 September 2014
  Abstract submission is now closed for the EHDN plenary meeting in Barcelona, but you can still register until 31 July. After that, registration will be subject to seating availability and may not be guaranteed. Urgent requests should be sent to: ehdn2014@euro-hd.net
- Neuroscience 2014 in Washington DC, USA, 15-19 November 2014