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EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

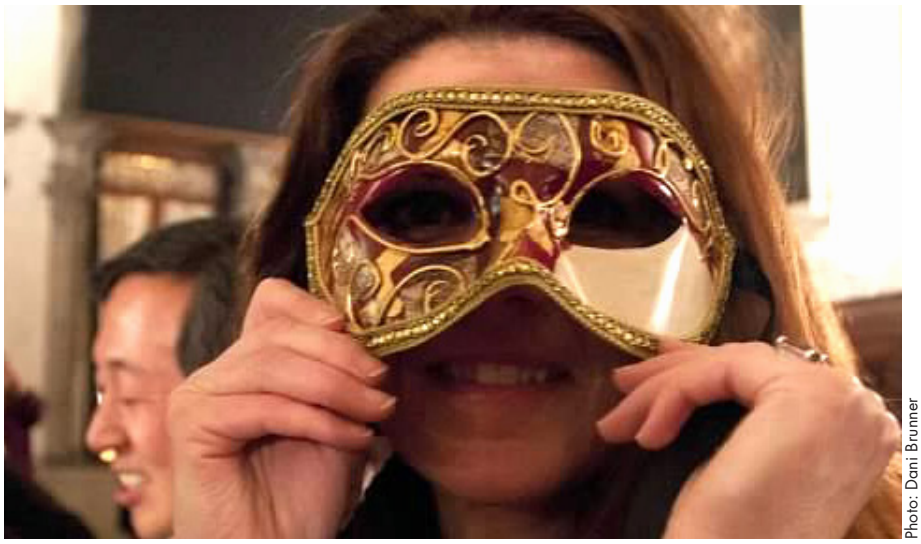

Photo: Dani Brunner

This year's Huntington's Disease Therapeutics Conference took place in Venice, Italy. Read more on page 3.

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Fellowship exchange programme announces first winners

Laura Spinney

Miriam Batule Dominguez

Jesús Pérez Pérez

Yury Seliverstov

This autumn the first three successful candidates in the EHDN Fellowship Exchange Programme will spend six weeks in their chosen host institutions improving their understanding of Huntington's disease (HD) clinical practice and research—knowledge the network hopes they will take back to their own countries and disseminate to their colleagues and collaborators.

The three fellows, whose names were announced in February, are Miriam Batule Dominguez of the Arnaldo Milián Castro Hospital in Santa Clara, Cuba, who will go to the University of Cambridge to work with the team of consultant neurologist Roger Barker; Jesús Pérez Pérez of the Hospital de la Santa Creu i Sant Pau in Barcelona, who will join Sarah Tabrizi's group at University College London; and Yury Seliverstov, who works in the neurogenetics department of the Russian Academy of Medical Sciences in Moscow, and who will join Michael Orth's team at the University of Ulm in Germany. All three are young neurologists specialising in movement disorders. Seliverstov is already involved in the network as a Russian language coordinator, and both he and Dominguez are working on research projects related to movement disorders. Pérez, meanwhile, has been involved in setting up a multidis-

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ciplinary HD clinic at his hospital. Each will receive €1500 plus travel expenses towards their stay.

The goal of the pilot project is to motivate, and facilitate the training of, young neurologists and psychiatrists working in HD, but also to help establish channels of communication and collaboration between institutions involved in HD. Among the criteria for candidate selection are that they come from countries needing to improve either their clinical understanding of HD, or their HD research base, or both. For Pérez, the fellowship will be a "superb opportunity to establish collaborative links with one of the most representative HD clinical research centres in the world". He added that, "It will also be a great chance to learn, and why not, to start a research collaboration between London and Barcelona."

Juliana Bronzova of EHDN's Central Coordination, who is overseeing the project, is delighted with the response—especially given that there was not much time to apply for this initial round. "It required real motivation on the part of the candidates, and eight people showed they had it," she said. "Of those, six were eligible. The most interesting part is that we had applications from outside the network," notably from Cuba. "We want to show that we're not just keen to support our own members," she added.

Host institutions also proved highly cooperative and eager to support the initiative. The three fellows are expected to file reports on their experiences by the end of 2013, and the EHDN executive committee will decide then whether the programme should continue to a second round.

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EHDN welcomes new grant manager

Laura Spinney

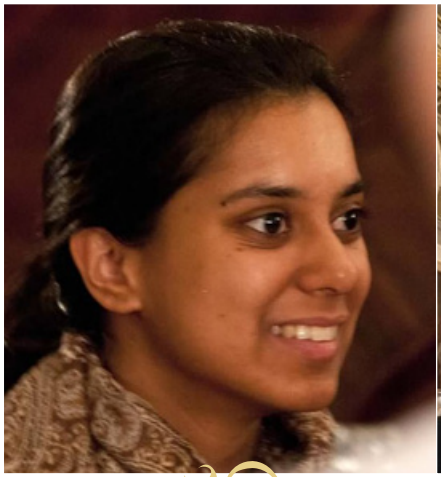
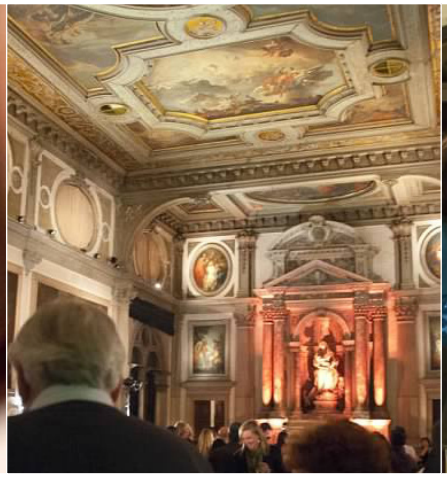
In April 2013 EHDN expanded its team to include a new member, Grant Manager Fionnuala Margreiter.

Fionnuala's mission is to increase the network's visibility to potential external partners, and to identify new funding opportunities for research and infrastructure support. More specifically, she's there to bring potential funding opportunities to the attention of EHDN members, and to encourage and support them in submitting proposals. She will provide a link with funding bodies at national and European levels, and help the network prepare for the European Commission's next framework programme for research and innovation, Horizon 2020, which is due to start on 1 January 2014. She will also explore potential collaborations with the Human Brain Project, a European attempt to improve understanding of the human brain that has been selected by the EC's Future and Emerging Technologies Flagship Programme to be funded over at least 10 years, to the tune of up to €100 million per year. Fionnuala, who is Irish, comes to the network from

Fionnuala Margreiter

the Austrian Tyrol, where she worked for the last eight years as a European Union and international project manager in life sciences at the CEMIT Center of Excellence in Medicine and IT in Innsbruck.

EHDN members who would like to discuss any potential funding opportunities should feel free to contact Fionnuala: fionnuala.margreiter@euro-hd.net


Progress in Venice

Simon Noble, Director of Scientific Communications, CHDI Management/CHDI Foundation

The Huntington's Disease Therapeutics Conference moved back to Europe in April, to the magical city of Venice, to encourage the attendance of European delegates. This was the eighth in the annual conference series and, with 285 participants, the largest yet.

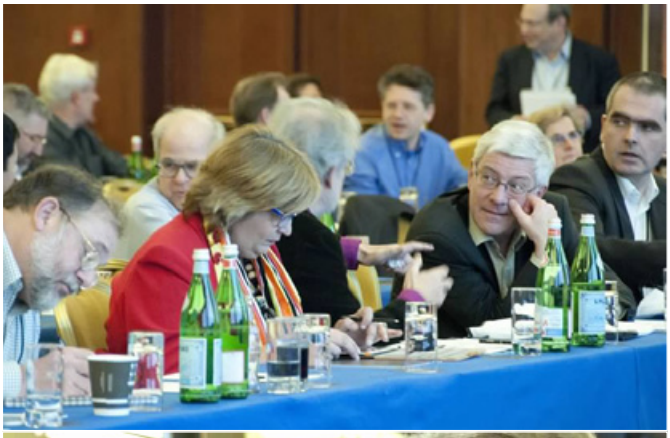
The 2013 meeting was notable for encouraging news of progress towards the clinic, beginning with an announcement that Roche has formed an alliance with Isis Pharmaceuticals to develop, for the clinic, its antisense oligonucleotide (ASO) approach to lowering huntingtin levels. For CHDI, which collaborated with Isis to develop the ASOs for HD, this was an important validation of their model to develop and derisk therapeutic programmes to the point where pharmaceutical companies are willing to step in.

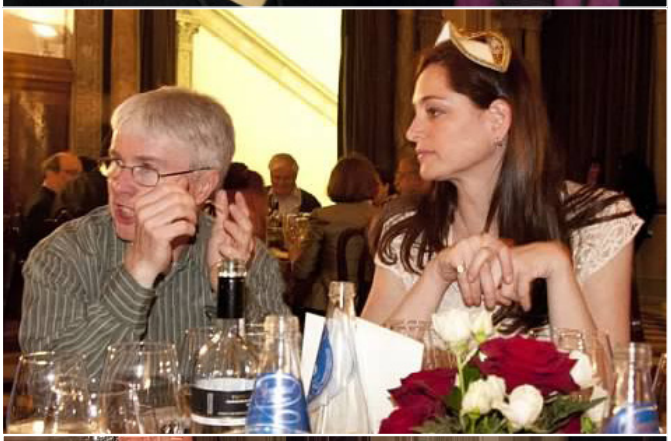
Margaret Zaleska of Pfizer described her company's efforts to evaluate an inhibitor of phosphodiesterase 10A (PDE10A) called MP-10. Preclinical work by CHDI has shown that PDE10A inhibition can improve dysfunctional corticostriatal connectivity in two mouse models of HD, R6/2 and Q175, suggesting that it could alleviate multiple symptoms in patients. Importantly, MP-10 has already been administered to humans in trials for other disorders, where it has proved to be safe and well-tolerated. Pfizer and CHDI are now planning human biology studies with MP-10 to expedite progress to clinical trial.

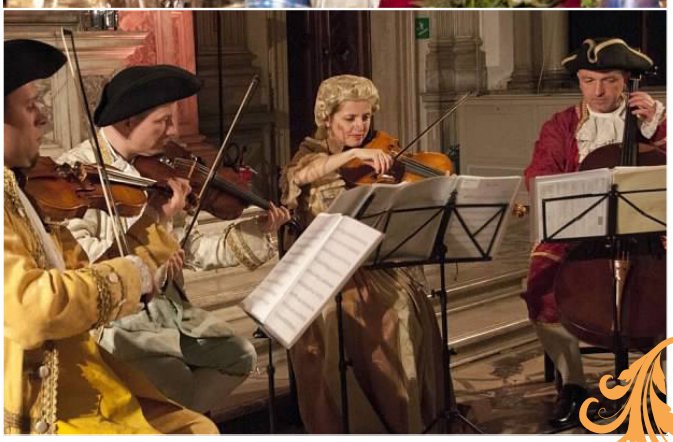
In a related talk, **Ken Marek** of the Institute for Neurodegenerative Disorders (IND) in New Haven, Connecticut, described his team's PET imaging work using striatal probes, which has shown that, as in rodent models, PDE10A expression diminishes with disease progression in humans. These findings suggest that PDE10A could provide a potential biomarker for the disease. IND and CHDI will now collaborate to measure PDE10A levels in HD patients differing in their number of CAG repeats and disease stage, in an adaptive study that will guide cohort selection.

Zaleska said that Pfizer will also conduct a related dose refinement study to evaluate occupancy of PDE10A in the striatum after oral administration of MP-10 to healthy volunteers. Most excitingly, Pfizer is planning the first trial of MP-10 in patients with early HD, to evaluate safety and tolerability and explore functional outcomes (cognitive, motor, corticostriatal function and apathy), that will begin before the end of the year. If all goes well, a proof-of-concept trial is planned for 2014.

CHDI scientists presented three late-stage programmes that are approaching clinical development. **Ladislav Mrzljak** explained that a kynurenine monooxygenase (KMO) inhibitor, CHDI246, "modulates favorably kynurenine pathway metabolites" in both rodent HD models and nonhuman primates, but that large species differences in its pharmacokinetic and pharmacodynamic profiles require further investigation.







The photos in this article were kindly provided by Dani Brunner.

Histone deacetylase (HDAC) 4 is "one of the most genetically well-validated targets, aside from huntingtin itself, that the HD community has seen", **Vahri Beaumont** told delegates, with work in Gill Bates' lab having shown phenotypic improvement in three HD mouse models that have been further engineered to knock down HDAC4. The sticking point, Beaumont said, is that the lead catalytic site inhibitor designed to date has not proved very effective in mouse models. A pharmacodynamic marker of target engagement is required to establish whether this is because such inhibitors are not a viable approach, or because the inhibitor in question is suboptimal.

The TrkB receptor promotes neuronal survival after activation by brain-derived neurotrophic factor (BDNF), a protein that is reduced in both HD patients and HD animal models. **Jonathan Bard** described work with two partial agonist monoclonal antibodies from Pfizer that activate the TrkB signalling cascade. This programme is now moving towards evaluation in animal models and Bard is hopeful that the antibodies (or alternative TrkB/BDNF strategies under investigation) will lead to improved synaptic function, neuroprotection and improvement in the HD phenotype.

These were just some of the developments presented at a meeting that gave much cause for optimism regarding the future of HD therapeutics.

Olivia Handley

Update: Enroll-HD

30 May 2013 marked an important milestone. It was the day the first Latin American patient was enrolled into ENROLL-HD.

As of the end of May, 684 participants had been recruited into ENROLL-HD in total, from 27 sites in the USA, Canada and Argentina. The first enrolling site, the University of Tennessee, is seeing its first follow-up participants.

ENROLL-HD will eventually combine the existing Registry and Cohort longitudinal clinical observation studies of HD into the first global study of the disease. Registry is a European study, while Cohort operates in North America and Australia. But ENROLL-HD will also include sites from the nascent Latin American network, Red Latinamericana de Huntington (RLAH).

In North America, all five Canadian sites have been initiated and are enrolling. Twenty-one US sites are enrolling, with ethical approvals in place for a further seven. Twenty-three sites are undergoing start-up, of which six have ethical approval (contract pending) and eight are under ethical review.

In April, an ENROLL-HD investigator meeting was held in Buenos Aires. The two-day meeting was attended by more than 35 site investigators and coordinators from Argentina, Peru and Chile. The first site initiation visit was completed for Frederico Micheli's unit at the Hospital de Clinicas José de San Martin in Buenos Aires in May, and participant recruitment has begun. Regulatory and ethical submissions are ongoing for the remaining Argentinian sites, and have commenced for Peru and Chile. The investigator meeting for Brazil will take place after the World Congress on Huntington's Disease in Rio de Janeiro in September.

In Australasia, the investigator meeting was held in Melbourne in June and was attended by over 20 investigators and coordinators from the five Australian sites and the two in New Zealand. It is anticipated that the first Australasian participant will be enrolled in July.

In Europe, the first half of 2013 saw significant progress in preparing for the transition of Registry sites into ENROLL-HD. Countries have been assigned to four phases of roll-out, and Belgium, Denmark, Germany, Italy, Ireland, Poland, Spain and the UK have already initiated theirs. Regulatory notifications have begun for Germany, Italy and Spain, with ethical submissions for these three countries planned for June and July.

Meanwhile, the EHDN team is working hard to prepare for the close-out of Registry. This involves increasing the frequency of site monitoring visits and completion of data coding (for medications, indications and comorbid conditions). It is important that each site's Registry database is 100 per cent closed before it undergoes transition, which means that all data must be monitored and coded, and all queries addressed. This requires considerable effort and collaboration on the part of EHDN staff and study sites. We would therefore like to take this opportunity to thank site staff for their continued support of the Registry-to-ENROLL-HD transition.

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

PBA-s training for ENROLL-HD

Jenny Callaghan, Language Area Coordinator, UK

Training for the short version of the Problem Behaviours Assessment for HD (PBA-s) is being rolled out to all investigators in the new ENROLL-HD study.

One of the core assessments in ENROLL-HD, the PBA-s is a semi-structured clinical interview assessing key behavioural symptoms of HD. It was developed by the EHDN's behavioural phenotype working group.

With ENROLL-HD being carried out in a large number of sites across the world, it is very important that the PBA-s and other core assessments are conducted in the same way at each site, so that the data collected are comparable. To that end, with the help of David Craufurd, lead facilitator of the behavioural phenotype working group and author of the original PBA, I have developed a PBA-s training programme.

Our training programme is interactive and combines theory and practice. We explain the key principles behind the items in the PBA-s, and give everyone an opportunity to apply the scoring criteria to some real-life video examples. The programme can be delivered face-to-face, at regional investigator meetings or ENROLL-HD site initiation visits, or online, via webinar.

The first stage in rolling out the PBA-s training programme for ENROLL-HD investigators has been to identify and train top-tier PBA trainers for each language area in ENROLL-HD, so that they can then pass on their training to investigators working in those areas.

In the summer of 2012 we trained top-tier trainers for the North American region. They have run 25 training sessions to date, and continue to run regular sessions as more North American sites join ENROLL-HD. Feedback from these training sessions has been very positive so far. Karen Anderson, an ENROLL-HD investigator from Georgetown University, said, "I found the training to be very straightforward and easily understood. The only difficulty I had was [in] understanding the regional accents in the videos, but the transcriptions really got around this. It's actually a lot of fun watching another clinician do an interview, something I don't get to see nearly as much as I would like."

The PBA training group in Buenos Aires

More recently, we have travelled to Buenos Aires to train top-tier trainers for Latin American countries, and we supported our Latin American PBA trainers at their inaugural regional investigator meeting in April. We are also assisting our Brazilian trainers to prepare for a training session at the upcoming Portuguese-speaking Latin American investigator meeting in September.

A PBA-s training workshop for top-tier PBA trainers in Europe was held in Manchester, UK, on 30 May, with representatives from countries including Italy, Spain, Germany and Denmark. We also ran PBA-s training sessions at a recent meeting of EHDN Language Area Coordinators, so that LanCos can help support top-tier trainers to deliver training in each language area of the network.

As the transition from Registry to ENROLL-HD progresses in Europe, we will continue to work with our top-tier trainers to implement training at all sites, to ensure that every site in ENROLL-HD has at least one trained PBA rater. As well as improving the quality of PBA-s data collected in ENROLL-HD, the behavioural phenotype working group hopes the training will increase awareness of the behavioural symptoms of HD.

With help from our top-tier trainers and colleagues in the working group, we also hope to build up a video library of PBA-s training materials in different languages, to allow our top-tier trainers to show real-life video clips in their native languages.

Jenny Callaghan

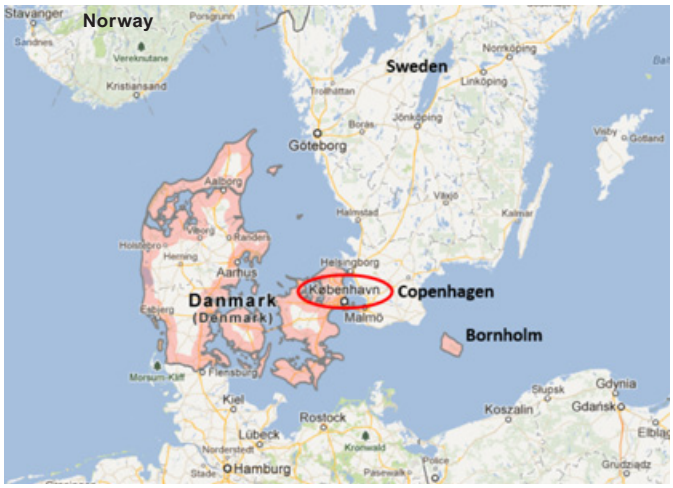
LanCo, LANGCO, Langco...?

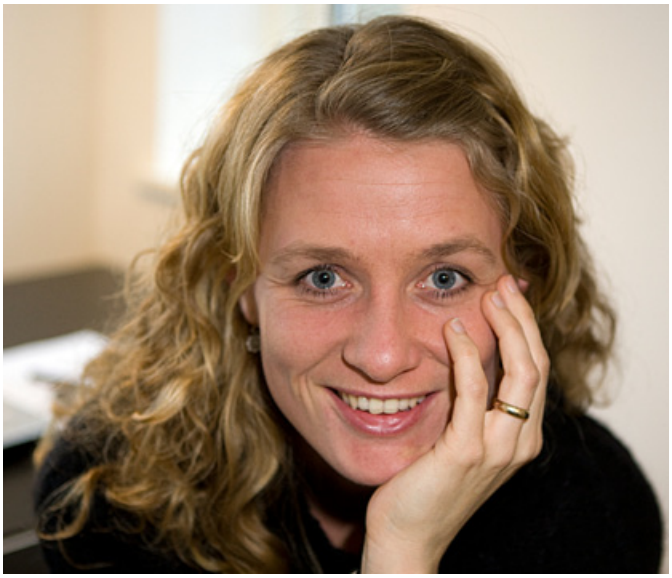
Mette Gilling Nielsen, Language Area Coordinator, Denmark

"Language Area Coordinator? What does that mean? Do you speak many languages?"

I was asked this question at a recent EHDN meeting by someone who was new to the network. Well I speak Danish, of course, and English, and I understand Swedish, Norwegian and some German. As far as my job is concerned, it is an advantage that I understand the other Nordic languages, but it is not a prerequisite and my task is essentially to coordinate EHDN-related activities in linguistically related countries. With LanCos, as we're called, in almost all the countries of Europe, the EHDN hopes to reduce as far as possible the linguistic and cultural barriers to its mission.

Like my colleagues in Sweden and Norway, I am employed as a Nordic LanCo, which means that we help each other when needed while being primarily responsible for our own countries. Some of the larger European countries have many Registry sites to monitor and support, and accordingly have several LanCos, whereas small countries like Denmark only have one. Denmark has three Registry sites, in Copenhagen, Aarhus and Odense. Copenhagen has participated in Registry since 2005 and is one of the largest sites in the EHDN network, whereas I launched Aarhus and Odense within the last six months.





Mette Gilling Nielsen

Most of the time I work virtually from my home in Copenhagen, but once a quarter I meet face-to-face with my EHDN colleagues in one of the larger European cities. I see my role as a full-time EHDN "octopus", because the job is so multifaceted. It is my responsibility to see that EHDN-facilitated projects such as Registry comply with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—Guideline for Good Clinical Practice (ICH-GCP), the protocol and the local laws in Denmark. This involves assisting in the writing of applications for ethical approval, monitoring data, training site personnel and visiting sites to support staff. I also organise an annual site investigator meeting where local Registry staff meet to be trained on Registry assessments, receive the newest HD research and clinical trial updates, and discuss possible collaborations.

> *"I consider it an important part of my job to communicate HD research and EHDN initiatives to the Danish HD community."*

I do that by writing quarterly articles for the Danish lay association magazine and ensuring that articles on HDBuzz are translated into Danish. I identify and mobilise resources for HD-related projects in Denmark, which involves collaborating with the Danish lay association, healthcare professionals and basic scientists to foster enthusiasm and unity. I also generate new ideas for HD projects. Currently, for example, I am trying to initiate two genetic research projects in collaboration with clini-

cians at the Copenhagen Registry site, and to modify the referral procedures of some Danish genetic clinics to ensure follow-up of HD patients takes place in Registry clinics.

In addition to our country-specific tasks, all LanCos are assigned to at least one of the 21 EHDN working groups, where our job is to help the lead facilitators organise their annual meetings, write minutes and keep the membership list and website up-to-date. I have been assigned to the biological modifier working group as primary LanCo, and to the genetic modifier working group as backup LanCo, since these fall within my areas of expertise and interest.

When I joined the network in 2011, the Scientific Strategic Plan for 2011–2015 was about to be implemented. The Scientific Planning Committee (SPC) and the Clinical Trials Task Force were established as part of that plan, and I was assigned to the SPC to provide practical support. It has been interesting to be part of the formation and development, and the scientific discussions, of the committee. In the last year the SPC has identified the clinical studies it feels should be performed to expedite the development of treatments for HD. The next step, to which I hope to contribute, will be to prioritise, initiate and manage those projects.

> *"I love the versatility of a job that in many ways reflects the twists and turns of my own career."*

I started out studying civil engineering, but the subject never really inspired me. 1997 was declared the Year of the Brain in Denmark, and attending the events designed to raise awareness of brain science convinced me to change path. I switched to applied physics and completed a project that involved analysing EEG data from brain-damaged patients. After a Masters in human biology, my interest turned to the genetic causes of heritable neurological disorders—the subject of both my PhD and a postdoctoral project. Nothing is more exciting to me than trying to explain a disease and intervene in it, but I felt that lab research could be frustrating, competitive and lonely. So when in 2011 I learned that EHDN needed a Danish LanCo, I saw it as an opportunity to apply my scientific training in a new setting, and I applied.

I have not regretted it. I believe my broad educational background helps me understand complex projects and communicate with people with different views and expertise. From my personal point of view, the flexibility of the job allows me to thrive in a challenging environment while still being team leader of my elder son's soccer team and sitting on the board of my younger son's kindergarten. And the diversity of the work makes it endlessly stimulating: variety, after all, is the spice of life.

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Photo: Dani Brunner

Dates for your diary

Save the dates for

- the 2013 World Congress on Huntington's Disease in Rio de Janeiro, Brazil, 15-18 September 2013
- CHDI's 9th annual HD Therapeutics Conference in Palm Springs, USA, 24-27 February 2014
- EHDN2014 in Barcelona, Spain, 19-21 September 2014