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EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Sven Pålhagen

EHDN2012: On the shoulders of giants

The 7th Plenary Meeting of the European Huntington's Disease Network (EHDN) took place in Stockholm, Sweden, from 14 to 16 September 2012, in conjunction with the 15th European Huntington's Disease Association (EHA) meeting, and drew 657 delegates from Europe, the Americas and beyond. The venue was Münchenbryggeriet, a former brewery on the island of Södermalm, across the water from Stockholm's City Hall. Anyone wandering out for a blast of autumn sunshine could therefore gaze upon the venue for the annual Nobel banquet before returning to the conference hall freshly inspired.

Welcome

Sven Pålhagen (Stockholm) of the local organising committee opened the meeting and introduced a man who clearly needs no introduction in Sweden. **David Lega** (Gothenburg), one-time Paralympian, businessman and politician, injected energy and optimism into the fledgeling plenary, as he presented model number five of his own wheelchair design and adroitly manipulated a bottle of water with his mouth (if he always had to carry straws around with him, he said, he would be that little bit more disabled). Lega, who was born with paralysed arms and limited use of his legs due to a congenital condition called arthrogryposis multiplex congenita (AMC), talked about the importance of adapting to disability—choosing your battles, not being afraid to fail, and taking strength from a support network that continually boosts your self-esteem. He was lucky enough to have been born to young parents who hadn't yet learned defeatism, he said, and he grew up surrounded by "happy eyes".

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Of course, disability comes in many different forms, and Astri Arnesen, speaking for EHA President **Beatrice De Schepper** (Moerbeke-Waas), reminded delegates of the devastation that Huntington's disease (HD) can inflict on a family. Thus armed with a goal and hope, the conference got down to business.

Hot topics

Following a hallowed plenary tradition, the scientific part of the meeting opened with a round-up of hot topics. First **Michael Hayden** (Vancouver) reminded the meeting that as many as five per cent of the general population may carry an "intermediate allele" or "grey area" HD gene, with 27 to 35 CAG repeats. The offspring of these people are at risk of inheriting an expanded CAG tract, with repeats in the 36-39 range, meaning that they could develop the disease in old age. In the past, this group of carriers may not have lived long enough to reach diagnosis, but in an ageing population that scenario is becoming increasingly common. The prevalence of HD is going to have to be revised upward as a result, genetic counselling will have to be made available to a broader category of people, and clinicians will have to adapt to the fact that the disease presents differently in late-onset patients.

Cristina Sampaio (Princeton) advocated smaller, more flexible clinicals trials that will produce results more quickly—"gazelles" as opposed to "mastodons". This means improving trial methodology, something her organisation, CHDI Foundation Inc., is investing a great deal of effort in. Assessing the risk-benefit ratio for a putative therapy is all-important, she said, and based on what is currently in the pipeline, the first treatments likely to come online will target the premanifest or manifest stages of the disease, not the earlier preclinical or presymptomatic phases. There is a difference between the reality and the dream, of course, and in an ideal world, said **Alexandra Dürr** (Paris), care should begin as early as possible, and be multidisciplinary. That is at least a theoretical possibility, since many studies have now documented changes long before diagnosis, including metabolic—reflected in early weight loss—and brain structural changes.

New frontiers

What light can basic biological research shed on HD? This session was designed to present the disease in a broader scientific perspective in the hope of suggesting new research leads. **Hugo Aguilaniu** (Lyon) kicked off with the notion that targeting longevity genes could prove a fruitful therapeutic approach. The molecular mechanisms mediating the body's response to stress in the form of caloric restriction, for example, could potentially impact on the functioning of such genes and provide protection against age-related disease.

Włodzimierz Krzyżosiak (Poznań) raised the possibility that not only the protein product of the mutant huntingtin gene, but also its RNA transcript, could be toxic to cells. The critical experiments have not been done to test this, but if the RNA does turn out to be toxic, there are methods available for blocking it.

What does the normal huntingtin protein (Htt) do? This is the $64,000 question, and **Ray Truant**'s (Hamilton) answer was that it is probably involved in the cell's

response to stress. He presented his "rusty hinge" hypothesis, according to which the protein's glutamine or CAG tract acts as a hinge, allowing it to fold. Expansion of that tract, combined with overphosphorylation of Htt, could cause the hinge to "rust" or become less flexible, impairing the protein's movement about the cell and, as a result, the cell's ability to respond to stress.

Elena Cattaneo (Milan) offered clues about the function of the huntingtin gene (*htt*) from its evolutionary history. This gene has been around in some form or other for 800 million years. Her experimental manipulations, which involve knocking it out in mouse embryonic stem cells and replacing it with its homologue from species belonging to different branches of the tree of life, suggest that one of its more ancient functions is to inhibit apoptosis, or programmed cell death. More recently, however, it may have acquired a role in regulating neural development. This function seems to be associated with the relatively youthful N-terminus of the protein, where the CAG tract lies. Cattaneo hypothesises, provocatively, that over the course of evolution, the expanding CAG tract may have acted as a driver of brain evolution.

Frédéric Saudou (Orsay) explained that Htt facilitates the transport of vesicles containing important chemicals through neurons. His work using microfluidic devices, which allow him to study different cellular compartments in isolation, suggests that Htt acts as a scaffold that recruits GAPDH to the vesicular surface. GAPDH is the all-important molecule that provides energy for vesicular transport, so this might explain why cell signalling is disrupted when mutant Htt (mHtt) fails to do its job properly.

Where next?

The biannual plenary is a chance to take stock and look to the future, and presenting EHDN's scientific strategy for 2011-2015 (www.euro-hd.net/html/disease/huntington/pubdocs/strategic-plan-full.pdf), **Juliana Bronzova** (Noordwijk) said that among the network's goals were improving the design of clinical trials so as to expedite them to useful conclusions, stimulating scientific collaboration and refocusing the objectives of the network's working groups (WGs), of which 20 are currently active. To that end, two new committees have been created, which along with the existing Scientific and Bioethics Advisory Committee (SBAC), will interact with the WGs and answer to the Executive Committee (EC). These are the Scientific Planning Committee, chaired by Gill Bates, and the Clinical Trials Task Force, chaired by Cristina Sampaio. EHDN has also instigated a medical writing support facility and, soon, a biostatistical support facility. Its new fellowship programme will be up-and-running by early 2013. The EHDN website will be revised to make it more visible.

Oliver Quarrell (Sheffield) gave an update on the work of the juvenile HD (JHD) WG. JHD, the onset of which occurs before the age of 20, accounts for five per cent of HD. It is associated with very large CAG repeat numbers—over 60 in about half of cases—and preliminary findings from magnetic resonance imaging (MRI) studies suggest that bigger expansions are associated with more rapid brain shrinkage, lending support to the idea that JHD has a shorter duration than adult-onset HD. If that is the case, Quarrell said, then the JHD population might be of interest to those designing clinical trials, because the effects of drugs might also be demonstrated more rapidly in this population. A new substudy of the European observational study REGISTRY is currently enrolling JHD patients in Europe, with 40 having been recruited to date.

Marian DiFiglia, Blair Leavitt and Marcy Macdonald

Gill Bates

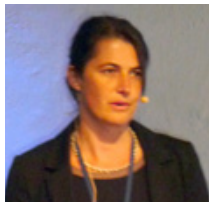
Bernhard Landwehrmeyer, Olivia Handley

Katia Youssov (Créteil), a member of the Advanced HD WG, described a version of the Unified Huntington's Disease Rating Scale (UHDRS) that has been adapted for advanced HD patients. The UHDRS-FAP was developed on the basis of a pilot study with 70 patients, and the group considers it superior to the UHDRS for this category of patient. It is more sensitive to remaining capacity, for example, while pushing back assessment of progression and floor effects to later in the disease.

Simon Brooks (Cardiff) explained that his group had found a "clear and beneficial" effect of exercise in the R6/1 mouse model of HD. This effect, which he thinks is cognitive rather than motor—affecting thinking speed—is reflected in reduced striatal atrophy in the mice. The optimal exercise dose has yet to be determined. However, **Monica Busse** (Cardiff) said that the evidence is now so clear that exercise is beneficial for HD patients, that the Physiotherapy WG, which she heads, is developing an evidence-based home exercise DVD for patients, called "Move Exercise".

Understanding the disease process

Gill Bates (London) described her group's attempts to find out how mHtt gets cleaved into pathogenic fragments in the cells. **Ellen Nollen** (Groningen) has identified genes in the worm *Caenorhabditis elegans* that prevent the harmful build-up of alpha-synuclein, the protein that accumulates in cells in Parkinson's disease (PD). Protein aggregation is a problem in both PD and HD, only in HD the protein in question is mHtt. One of the genes Nollen has identified, *tdo-2*, produces a protein whose human homologue, TDO, she thinks could be an interesting target for an HD drug. Interestingly, TDO is related to the enzyme KMO, which is already being investigated as a potential target.



Erich Wanker (Berlin) described his group's attempts to map, systematically, all the cellular interactions of proteins known to be involved in potentially related neurodegenerative diseases, including Alzheimer's disease, PD and HD. And **Nicholas Perentos** (Cambridge) gave an update on progress in a new sheep model of HD. Due to its large brain, which is anatomically more similar to the human brain than that of a mouse, this could prove very valuable in studying HD-related brain changes, and in testing therapies that require some kind of special brain delivery, such as an injection.

Observing HD

Olivia Handley (London) described how REGISTRY and its sister study COHORT—which covers America, Australia and New Zealand—will be merged as of 2013 into a new study called ENROLL-HD. As ENROLL-HD's Global Project Manager, she told the conference that the new study already has three sites that are actively recruiting, and 37 participants, and continues to roll out to new sites all over the world. Meanwhile, the number of participants in REGISTRY was announced to be tantalisingly close to the 10,000 landmark, at 9,982.

Sarah Tabrizi (London) gave an update on the major observational study TRACK-HD, which will now be


Sarah Tabrizi

succeeded by TRACK-ON. TRACK-HD completed 36 months in December 2011, and the as yet unpublished 36-month data show significant change on a range of motor, cognitive and brain imaging tasks in those premanifest HD gene carriers who were less than 10.8 years from their predicted onset at baseline (where onset is predicted on the basis of age and CAG repeat number). This means that, for the first time, it is possible to assess a premanifest individual using such tests, and accurately predict their onset.

Andrea Varrone (Stockholm) and **Rachel Scahill** (London) told delegates that the brain imaging techniques positron emission tomography (PET) and MRI had now proved their worth as robust and meaningful markers of disease progression. **Michael Orth** (Ulm) reported that changes in activity in the brain's default mode network—that circuit which is active when our brains are "idling", and which goes quiet when we execute a task—might be sensitive to disease progression, starting pre-diagnosis.

He has conducted a small, cross-sectional study using functional MRI (fMRI), and finds that, in premanifest carriers, unlike in healthy controls, the network doesn't completely shut down during performance of a task. **Nellie Georgiou-Karistianis** (Clayton) reported that working memory tasks can be used to detect change in the relevant brain networks over 18 months, using fMRI in premanifest patients.

Julie Stout (Clayton) described her group's efforts to develop a brief, sensitive cognitive assessment test battery for clinical trials in early HD, based on what has worked in large observational studies like TRACK-HD.

Those tests need to reflect growing understanding of HD pathophysiology and progression, and to be clinically meaningful and relevant to affected individuals' day-to-day functioning and quality of life, she said. **Anne-Catherine Bachoud-Lévi** (Créteil) said that there was room for new cognitive tests that were even more sensitive to disease progression than existing ones, and that could be administered more rapidly. Based on an ongoing pilot study that her group is conducting, she suggested that very simple tasks—ones involving picture-naming and basic arithmetic, for example—could be appropriate. Meanwhile, **Ellen 't Hart** (Leiden) has found cognitive and general functioning differences between the two motor subtypes of HD—choreatic and hypokinetic-rigid—with the former performing better on both.

Therapy: bright hopes

Fetal grafts continue to show therapeutic promise, **Patrik Brundin** (Grand Rapids) told the conference, but a less morally fraught alternative, induced pluripotent stem cells (iPSC), are causing much excitement—if not yet as a therapy, then as a valuable tool for understanding HD. These cells can be made from a person's skin cells, then reprogrammed to develop into a wide range of other cell types which can later be grafted back into the person—without risk, in theory at least, of immune rejection. In the case of HD gene carriers, iPSC will need to be genetically "corrected" before being grafted. But the uncorrected cells could also be of interest, as **Leslie Thompson** (Irvine) explained. The National Institute of Neurological Disorders and Stroke (NINDS)/CHDI stem cell consortium, which she heads, has generated iPSC lines from HD gene carriers and healthy

controls, and shown that many cellular processes in uncorrected iPSC are affected by the HD mutation in a CAG repeat number-dependent manner. The cellular assay that appears to be most sensitive to the number of CAG repeats is the calcium signalling response to stress. This could potentially be used, therefore, in testing new HD drugs. **Lisa Ellerby** (Novato) presented a multicentre, collaborative effort to study HD using iPSC. Not only has her group shown that it is possible to correct the HD genotype, she said, but that correction is reflected in a corrected cellular phenotype. Levels of brain-derived neurotrophic factor (BDNF), which are low in HD cells, return to normal in the corrected ones, for example. The next step for her group is to transplant the corrected cells into a mouse model of HD, to see if this corrects the phenotype at the level of the organism.

The other bright hope for future therapy is huntingtin-lowering drugs, aka gene silencing technology. Htt can be lowered in cells, either by blocking the DNA of the mutant *htt* gene, or by blocking its RNA transcript, and keynote speaker **Beverly Davidson** (Iowa City) and colleagues have focused on the latter. In HD mouse models treated with so-called RNA interference (RNAi) techniques, they have shown that the mice live longer, and show less neuronal damage and better neurological function than untreated controls. Moving a step closer to the clinic, they have now shown that the technique is safe in rhesus macaques, while reducing Htt levels by half. An alternative approach, based on antisense oligonucleotides (ASOs) has been shown by Donald Cleveland's group in San Diego to produce improvement in HD mice, when injected directly into the brain, and to spread further through the brain than RNAi-based drugs. The question remains, however, whether ASOs are able to reach the deep basal ganglia, which are affected early in HD. The first clinical trials of RNAi-based drugs are due to get underway in 2013.

The drug pipeline

Douglas Macdonald (Los Angeles) described seven different Htt-lowering technologies that CHDI is actively pursuing, some of which are close to clinical trial. These include DNA-based drugs that are injected into the spinal fluid, and RNA-based ones that are injected directly into the brain. **Andrea Caricasole** (Siena), presented Siena Biotech's drug Selisistat, which is being tested in the European PADDINGTON study. In theory, and in preclinical studies, Selisistat prevents mHtt from accumulating in cells by inhibiting the enzyme sirtuin 1. Sirtuin 1 removes the acetyl tags from mHtt, where the tags act as a signal to the cell to get rid of the harmful protein. **Chris Schmidt** (Groton) described an inhibitor of PDE10A that is currently being tested, in a collaboration between CHDI and his company, Pfizer, in mouse models of HD. PDE10A is a subtype of the phosphodiesterase PDE10, an enzyme that clears away signalling molecules from neurons once they have been received from nearby neurons via a synapse or chemical junction. Preventing it from doing so could increase the intensity of the signal and so, potentially, compensate for the impaired synaptic function in HD. A clinical trial will hopefully get underway next year. **Frank Gray** (Stevenage) is interested in a different phosphodiesterase, PDE4, which is also involved in signalling at synapses. In neurons grown *in vitro*, a PDE4 inhibitor made by his company, GlaxoSmithKline, produced improvements in functions related to learning. Gray thinks the inhibitor will potentially be useful for treating the cognitive

symptoms of HD. **Josef Priller** (Berlin) described a trial called Action-HD which is designed to test the effects of the drug buproprion—marketed as Wellbutrin—on apathy in HD. Apathy, or lack of motivation and emotional blunting, is a major problem in HD. Action-HD began recruiting in May 2012 at four sites in Germany. Last but not least, **Julie Stout** presented Reach2HD, a phase 2 trial of the copper-reducing drug PBT2, produced by Australian company Prana Biotechnology.

Business meeting

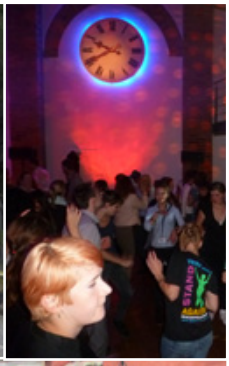
There was plenty of network business to discuss, beginning with the approval of amendments to the constitution (www.euro-hd.net/html/network/project/constitution). Following the network's 2012 elections, **Bernhard Landwehrmeyer** (Ulm) and **Joaquim Ferreira** (Lisbon) were re-elected to the EC, while **David Craufurd** (Manchester), **Ralf Reilmann** (Münster) and **Sarah Tabrizi** (London) were elected to it for the first time. **Gill Bates** (London), **Pierre Krystkowiak** (Amiens) and **Sheila Simpson** (Aberdeen), rotating out, were thanked for their valuable contributions. **Bernhard Landwehrmeyer**, who was re-elected as committee chair, announced that, though he will stand for the full four years of his second term, he will only be available as chair for two. **Jean-Marc Burgunder** (Bern) replaces **Gill Bates** as co-chair. **Chris Frost** (London), **Flaviano Giorgini** (Leicester), **Andrea Nemeth** (Oxford), **Hugh Rickards** (Birmingham), **Jennifer Thompson** (Manchester) and **Patrick Weydt** (Ulm) were elected to the SBAC, replacing **Lesley Jones** (Cardiff), **Anne Rosser** (Cardiff), **David Craufurd** and **Ralf Reilmann**, who along with **Bernhard Landwehrmeyer**, were thanked warmly for their input.

Bernhard Landwehrmeyer announced that an iPad would be awarded to the site that recruited the 10,000th participant in REGISTRY, to be used in study-related activities. The winning site turned out to be Münster in Germany, the landmark being reached just a few days after the meeting, on 18 September.

Daniela Rae (Aberdeen) presented the guidelines that were published by the Standard of Care WG early in 2012. The result of the group's systematic documentation and appraisal of all the care models available in Europe, the guidelines are based on the principle of a multidisciplinary managed care network.

Matt Ellison (Coventry), who watched his father lose his battle with HD and founded the Huntington's Disease Youth Organization, HDYO (pronounced "HD-Yo"), in February 2012, made a plea for better access to the HD community and information for young people affected by the disease. HDYO already has a 70-strong team and over 1000 friends on Facebook, and is growing fast.

Charles Sabine (Gloucestershire), HD gene carrier and advocate, echoed Ellison's sentiments as he closed EHDN2012 with a moving reminder to delegates of the importance to affected families of their continuing



efforts to understand and treat the disease. Little by little, he said, understanding was diluting fear, and each generation had less to fear than the last. In 2012, it was no longer possible for a doctor to tell a gene carrier, at the point of diagnosis, that his or her disease was incurable.

Thanks...

...to all those who made EHDN2012 the success that it was, including the local organising committee (**Sven Pålhagen**, **Martin Paucar**, **Maria Björkqvist** and **Åsa Petersen**), the programme committee chaired by **Christian Néri**, and EHDN Central Coordination (**Jamie Levey**, **Katrin Barth**, **Jeton Iseni** and others). Thanks to **Ed Wild** and **Jeff Carroll** for lightening the proceedings with their nightly "sci-entertainment". Thanks to the **City of Stockholm** for welcoming delegates to a reception in the magnificent City Hall. And special thanks to sponsors **BioRep**, **Ipsen**, **NeuroSearch**, **Lundbeck**, **Medesis**, **AOP Orphan**, the **City of Stockholm**, and in particular the **CHDI Foundation**, without whom neither the network nor the meeting would have been possible.

Thanks also go to **Gill Bates**, **Jenny Morton** and the rest of the editorial team who have produced this newsletter over the last four years. In an attempt to respond to readers' evolving needs, the new editorial team, **Laura Spinney** and **Gabriele Stautner**, have introduced some changes. The newsletter will now appear three times a year (in November, March and July) and be slightly shorter, no longer including lay summaries of scientific research or a meeting agenda. All feedback on the new format, as well as ideas for stories of potential interest to network members, are welcome and should be sent to newsletter@euro-hd.net

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, www.wchd2013.com

and for EHDN2014 in Barcelona, Spain, September 2014